UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE: JOHNSON & JOHNSON TALCUM POWDER PRODUCTS MARKETING, SALES PRACTICES, AND PRODUCTS LIABILITY LITIGATION	**Civil Action No. 3:16-md-2738-MAS-RLS** **MDL No. 2738**
THIS DOCUMENT RELATES TO ALL CASES	

THE PLAINTIFFS' STEERING COMMITTEE'S MEMORANDUM OF LAW IN OPPOSITION TO DEFENDANTS JOHNSON & JOHNSON AND LLT MANAGEMENT, LLC'S MOTION TO EXCLUDE THE PLAINTIFFS' EXPERTS' OPINIONS REGARDING BIOLOGICAL PLAUSIBILITY/MECHANISM

Table of Contents

TABLE OF AUTHORITIES

Cases

Statutes

Rules

Other Authorities

The Plaintiffs' Steering Committee ("PSC") submits this memorandum in opposition to Defendants Johnson & Johnson and LLT Management, LLC's (together, "J&J") motion to exclude the PSC's experts' opinions related to biological plausibility and mechanism (Dkt. No. 33013-1) ("Motion" or "Mot.").[1] For the foregoing reasons, this Court should once again deny J&J's Motion.

I. INTRODUCTION

After extensive briefing by the parties and live testimony from the PSC's experts, Judge Wolfson found that they offered a sufficiently supported mechanism by which talcum powder can travel to the ovaries, fallopian tubes, and peritoneal cavity and lead to ovarian cancer. Dkt. No. 13186 at 94-95. Citing black letter law, Judge Wolfson explained: "Bradford Hill and *Daubert* do not require that an expert *prove* the proposed mechanism – they need only provide reliable support that demonstrates that the mechanism is *plausible*." Dkt. No. 13186 at 94 (emphasis in original). As to the PSC's experts, Judge Wolfson then held: "The Court is satisfied that these experts, based on the various studies and their past scientific experience and knowledge, have done so under *Daubert*." *Id.* Having found the PSC's experts

[1] This opposition specifically relates to the biological plausibility opinions of Drs. Shawn Levy, Arch Carson, Michele Cote, Bernard Harlow, Daniel Clarke-Pearson, Sarah Kane, Anne McTiernan, Patricia Moorman, Laura Plunkett, Jack Siemiatycki, Sonal Singh, Rebecca Smith-Bindman, Ellen Blair Smith, and Judith Wolf. Mot. at 1 n.2.

sufficiently supported their opinions, Judge Wolfson held that J&J's attacks on the scientific literature went to weight and not admissibility.

J&J's refiled brief on biological plausibility is akin to an untimely motion for reconsideration. J&J fails to identify any point on which Judge Wolfson "failed to adhere to Rule 702" or any "new science" justifying reversal.[2]

J&J accuses Judge Wolfson of applying too low a legal standard on biological plausibility. Mem. at 5. Trying to fit this argument within the requirements of Rule 702, J&J argues that Rule 702 "require[s] more than the mere speculation that Judge Wolfson found sufficient." *Id.* J&J improperly conflates proof of the merits with proof of reliability under Rule 702, and once again, advocates for an incorrect level of proof for biological plausibility.

Judge Wolfson did not base her opinion on mere speculation. She found that the PSC's experts "provided a solid basis for their theory" of biological plausibility based on the scientific literature. *In re Johnson & Johnson Talcum Powder Prod. Mktg., Sales Pracs. & Prof. Litig.*, 509 F. Supp. 3d 116, 174-75 (D.N.J. 2020). What J&J quibbles with, as it did before, is the standard for biological plausibility.

Biological plausibility is only one of nine Bradford Hill factors, and it is not intended on its own to prove causation. As a result, while the overall causation inquiry asks whether it is more likely than not that perineal use of talcum powder

[2] Memorandum Order, ECF No. 32122.

can increase the risk of epithelial ovarian cancer, biological plausibility asks "whether the hypothesized causal link is credible in light of what is known from science and medicine about the human body and possibly offending agent."[3] All that is required is that the mechanism is plausible (or makes sense) based on the evidence. Judge Wolfson correctly applied this standard. *Id.* at 174-175.

The revisions to Rule 702 did not change the standard for biological plausibility. The revisions simply clarified that an expert's opinions must be reliable by a preponderance of the evidence. Judge Wolfson properly found the PSC's experts' opinions met this standard. *Id.* at 187.

The Rule 702 revisions also did not eliminate a court's ability to ascribe expert challenges to weight. The 2023 Committee Notes make clear that "once the court has found it more likely than not that the admissibility requirement has been met, any attack by the opponent will go only to the weight of the evidence."[4] That is precisely what Judge Wolfson held. Judge Wolfson found the PSC's experts' general causation opinions, including biological plausibility, were reliable and based on sufficient evidence, and thus, J&J's challenges went to weight.

Indeed, the science supporting the PSC's experts' biological plausibility opinions has only strengthened since Judge Wolfson's 2020 order. There are

[3] *Milward v. Acuity Specialty Prods. Grp.*, 639 F.3d 11, 25 (1st Cir. 2011).

[4] Fed. R. Evid. 702, committee notes (2023).

additional studies showing talc causes chronic inflammation and new evidence of the presence of talc in ovarian tissue further supporting migration. The PSC's experts' opinions are also consistent with Health Canada's 2021 Screening Assessment on Talc[5] and the 2024 conclusion of the International Agency for Research on Cancer (IARC) of "**strong mechanistic evidence that talc exhibits key characteristics of carcinogens in human primary cells and experimental systems**."[6]

Like before, J&J simply offers different opinions based on the same evidence and disputes the PSC's experts' reliance on and interpretation of specific studies. As Judge Wolfson correctly found, these challenges go to the weight of the evidence, not exclusion under *Daubert*, and are dealt with on cross-examination before a jury.[7] J&J's Motion on biological plausibility should be denied in its entirety.

---

[5] Health Canada, Screening Assessment Talc (April 2021)) at 34 (**Exhibit 1**) ("[T]he available animal and human studies…clearly indicate that particles, including talc, may transfer from the vagina to the fallopian tubes and ovaries following perineal application. Recent research with respect to specific mechanisms (inflammation and/or tumor precursor events) add increased support to the biological plausibility.").

[6] *IARC Monographs* evaluate the carcinogenicity of talc and acrylonitrile *IARC Monographs* Volume 136," Questions and Answers (July 5, 2024) (**Exhibit 2**).

[7] *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 596 (1993); *Karlo v. Pittsburgh Glass Works, LLC*, 849 F.3d 61, 81 (3d Cir. 2017); *In re TMI Litigation*, 193 F.3d 613, 664, 665 (3d Cir. 1999); *Milward*, 639 F.3d at 22.

II. JUDGE WOLFSON APPLIED THE CORRECT LEGAL STANDARD[8]

J&J strains to fit its refiled brief within the bounds of this Court's April 30, 2024 Order,[9] arguing that Judge Wolfson applied a standard for biological plausibility that is contrary to the revisions of Rule 702 because she did not require proof of mechanism. Mem. at 5. Rule 702 has nothing to do with the level of proof required to demonstrate biological plausibility on the merits. Rule 702 simply requires that an expert is qualified and his or her opinions are relevant and reliable by a preponderance of the evidence.[10] Judge Wolfson correctly applied this standard.[11]

Judge Wolfson first acknowledged that the PSC's experts' opinions were appropriately "premised on their understanding that talc contains asbestos and other heavy metals."[12] She then assessed the studies that the PSC's experts relied on that

---

[8] The PSC incorporates the *Plaintiffs' Steering Committee's Brief Regarding the Rule 702 Standard* ("Rule 702 Brief," ECF No. 32994) and its *Memorandum of Law in Response and Opposition to Defendants Johnson & Johnson and Johnson & Johnson Consumer, Inc.'s Motion to Exclude Plaintiffs' Experts' Opinions Related to Biological Plausibility* (ECF No. 10065).

[9] *See* Memorandum Order, ECF No. 32122 (requiring new *Daubert* briefing to identify either "(1) that Chief Judge Wolfson's previous Opinion demonstrably fails to adhere to Rule 702 as clarified by the 2023 amendments; or (2) new science is shown to directly contradict or challenge Chief Judge Wolfson's previous findings.")

[10] Rule 702 Brief at 2-4.

[11] *Id.* at 8-16.

[12] *In re Johnson & Johnson*, 509 F. Supp. 3d at 172. Judge Wolfson found the PSC's experts "can reasonably rely on the assumption that talc contains asbestos" because she permitted Dr. Longo to testify that J&J talc contains asbestos. *Id.* at 172, n.39. New evidence also supports this assumption including, additional testing by Dr. Longo and the FDA's 2019 finding of asbestos in J&J's baby powder. Dyer, Owen. Johnson & Johnson Recalls its Baby Powder after FDA Finds Asbestos in Sample. BMJ 2019 (**Exhibit 3**); Longo 3rd Supp. Report (Nov. 17, 2023) (**Exhibit 4**).

show particles can move up from the vagina to the fallopian tubes and ovaries, concluding that "the various studies [combined with] their past scientific experience and knowledge" made the PSC's experts' opinions on migration reliable.[13] Judge Wolfson also assessed the evidence supporting the PSC's experts' opinions that exposure to talc can lead to chronic inflammation, finding that "Plaintiffs' experts provided a solid basis for their theory" and met the reliability standard under *Daubert*.[14]

J&J argues that Judge Wolfson was required to find that Plaintiffs proved the merits of biological plausibility based on preponderance of the evidence. Mem. at 5. That is incorrect. "Proponents of expert testimony do not 'have to prove their case twice – they do not have to demonstrate to the judge by a preponderance of the evidence that the assessments of their experts are correct, they only have to demonstrate by a preponderance of the evidence that their opinions are reliable."[15]

Indeed, "[t]here is an important difference between what is unreliable support and what a trier of fact may conclude is insufficient support for an expert's

[13] *In re Johnson & Johnson*, 509 F. Supp. 3d at 174-175.

[14] *Id.* at 175.

[15] *In re Processed Egg Prods. Antitrust Litig.*, 82 F. Supp. 3d 412, 416 (E.D. Pa. 2015); *see also U.S. v. Mitchell*, 365 F.3d 215, 244 (3d Cir. 2004) ("*Daubert* does not require that a party who proffers expert testimony carry the burden of proving to the judge that the expert's assessment of the situation is correct.").

conclusion."[16] Because Judge Wolfson held that the PSC's experts met the reliability threshold, it is the jury that will decide whether the experts' biological plausibility opinions are correct. Judge Wolfson explained: "Where, as here, the causation experts' opinions are based on facts, a reasonable investigation (including documented findings), and traditional technical/mechanical expertise, and the experts provide a reasonable link between the information and procedures they use and the conclusion reached, the *Daubert* requirements are met."[17]

Judge Wolfson also applied the correct standard for biological plausibility.[18] Biological plausibility asks whether given what we know about the disease in question and possible pathogenic mechanisms, does the association make sense.[19] Biological plausibility is not the same as biological proof or certainty.[20] As a result, it is not intended by itself to prove causation.[21] Thus, the PSC's experts "need not

[16] *Milward*, 639 F.3d at 22.

[17] *In re Johnson & Johnson*, 509 F. Supp. 3d at 187.

[18] *Id.* at 174-175.

[19] Sir Austin Bradford Hill, "The Environment and Disease: Association or Causation?," *Proc R Soc Med* 58(5): 295-300 (1965), at p. 298, **Exhibit 5**; Rothman et al., "Modern Epidemiology," (3d Ed. 2008) at p. 28-29, **Exhibit 6**; *Milward*, 639 F.3d at 25; *In re Johnson & Johnson*, 509 F. Supp. 3d at 174-175.

[20] *In re Abilify (Aripiprazole) Prods. Liab. Litig.*, 299 F. Supp. 3d 1291, 1308 (N.D. Fla. 2018) ("[B]iological plausibility is not the same as biological certainty."); Michael D. Green, *et al.*, *Reference Manual on Scientific Evidence*, at 604-05 (3d Ed. 2011); *In re Johnson & Johnson*, 509 F. Supp. 3d at 174.

[21] *Milward*, 639 F.3d at 25.

prove the biological means by which [talcum powder] acts in the body."[22] Instead, "where a hypothesis has been deemed plausible and credible in the relevant medical literature. . .it is reasonable to admit that hypothesis."[23]

As a result, at the *Daubert* stage, the PSC's experts are "not required to show that a mechanism has been definitely established. Instead [they] just need[] to show that the methodology [they] used to arrive at [their] opinion is sufficiently reliable."[24] That is precisely what Judge Wolfson found.[25]

The cases J&J cites do not apply a different standard. Instead, those courts found that the experts' causation opinions were not based on reliable methodologies.

---

[22] *In re Abilify*, 299 F. Supp. 3d at 1308; *In re Neurontin Mktg.*, 612 F. Supp. 2d 116, 145, 149 (D. Mass. 2009) (biological plausibility opinion supported despite "robust debate in the scientific community"); *In re PPA Prods. Liab. Litig.*, 289 F. Supp. 2d 1230, 1247 (W.D. Wash. 2003) ("The fact that the mechanism remains unclear does not call the reliability of the opinion into question" and citing *Daubert*); *In re Fosamax Prods. Liab. Litig.*, 645 F. Supp. 2d 164, 183 (S.D.N.Y. 2009) ("That the mechanism remains unknown does not mean that the one proposed by the PSC's experts is not widely accepted as plausible."); *In re Fosamax Prods. Liab. Litig.*, No. 11-5304, 2013 WL 1558697, *3 (D.N.J. Apr. 10, 2013) (fact that mechanism had not "been proven with human data" was not fatal to opinion).

[23] *Bartoli v. Novartis Pharms. Corp.*, No. 3:13-0724, 2014 U.S. Dist. LEXIS 52956, *23 (M.D. Pa. Apr. 17, 2014); *see also In re Zoloft Prods. Liab. Litig.*, 26 F. Supp. 3d 466, 469-70 (E.D. Pa. 2014) (finding a plausible mechanism of action where Zoloft "may" produce the adverse outcomes); *In re Fosamax*, 2013 WL 1558697 at *3 (defining biological plausibility as "coherence with existing knowledge").

[24] *In re Fosamax*, 2013 WL 1558697 at *6 (citing *Milward*, 639 F.3d at 15); *In re Roundup Prods. Liab. Litig.*, No. 16-MD-02741-VC, 2018 WL 3368534, at *17 (N.D. Cal. July 10, 2018); *see also Karlo v. Pittsburgh Glass Works, LLC*, 849 F.3d 61, 81 (3d Cir. 2017) (reliability standard "is 'lower than the merits standard of correctness'"); *In re Avandia Mktg. Sales Practices and Prods. Liab. Litig.*, No. 2007-MD-1871, 2011 WL 13576, at *9 (E.D. Pa. Jan. 4, 2011) (admitting expert testimony where "hypotheses about plausible mechanisms are based on scientific data about both the links between Avandia and lipid profiles and the connections between lipid profiles and outcomes").

[25] *In re Johnson & Johnson*, 509 F. Supp. 3d at 175.

Soldo v. Sandoz Pharms. Corp., 244 F. Supp. 2d 434 (W.D. Pa. 2003) quoted a passage from another district court case where the plaintiff, in opposing summary judgement, failed to provide any affirmative evidence demonstrating an association between the agent and the alleged medical condition. *Id.* at 533-34. The court found that this left plaintiff "with anecdotal reports and an untested theory [of mechanism] as evidence of causation," which the court found to be insufficient. *Id.* at 534.

Here, the PSC's experts do not rely solely on biological plausibility. They conduct a comprehensive Bradford Hill analysis of the substantial scientific evidence relevant to genital talcum powder use and ovarian cancer, considering each of the nine factors, which Judge Wolfson found to be reliable.[26]

Wade-Greaux v. Whitehall Lab'ys, Inc., 874 F. Supp. 1441 (D.V.I. 1994), also does not apply a different standard. There, the issue was whether bird cell studies could be used as mechanistic proof of what happens in humans. The court concluded that under the facts of that case they could not. *Id.* at 1464. The *Wade-Greaux* court also found the expert was not qualified and made unsupported assumptions in his bird cell testing, which made his opinions speculative. *Id.*

Similarly, in *In re Acetaminophen – ASD-ADHD Prod. Liab. Litig.*, MDL No. 3042, 2023 U.S. Dist. LEXIS 224899 (S.D.N.Y. Dec. 18, 2023), the court excluded

[26] *Id.* at 162-185.

an expert's general causation opinions after finding that the "analytical construct" he used, known as AOP 20, was an unreliable method to demonstrate acetaminophen use by pregnant women causes ASD and ADHD in their children. *Id.* at *113-114. The court found that because AOP 20 is used to show mercury (not acetaminophen) exposure causes developmental effects different from ASD and ADHD, something more was needed to show its relevance. *Id.* at *115. After assessing the expert's reliance on other studies, the court determined that his methodology was flawed because he "cherry-pick[ed] isolated findings, ignore[ed] inconsistent findings, and disregard[ed] limitations expressed by a study's authors as well as generally accepted statistical principles." *Id.* at *117-121.

Here, the PSC experts' opinions on mechanism are well supported by substantial and reliable evidence in humans. As a result, they readily meet the Rule 702 requirements for reliability and the standards for biological plausibility.

III. THE PSC'S EXPERTS' BIOLOGICAL PLAUSIBILITY OPINIONS REMAIN RELIABLE AND ADMISSIBLE

A. THE PSC'S EXPERTS APPROPRIATELY CONSIDER SUBTYPES

J&J reasserts its argument that the PSC's experts fail to consider the different subtypes of ovarian cancer and accuses Judge Wolfson of "barely address[ing]" this argument. Mem. at 9. Not so.

Judge Wolfson expressly acknowledged J&J's argument that the PSC's experts "'ignore[] the undisputed fact that ovarian cancer is not a single disease, but instead a number of different diseases, all with different genetic origins, risk factors, and treatments.'"[27] However, Judge Wolfson correctly rejected it:

> The testimony of Plaintiffs' experts demonstrates that their opinions rest on good grounds and considered scientific evidence to conclude that the association is specific to ovarian cancer. The experts do not opine as to any link between talc use and any other genital cancer. Their findings are limited to epithelial ovarian cancer. While epithelial ovarian cancer may have various subtypes, Defendants have not sufficiently demonstrated that Plaintiffs' findings are unreliable. Defendants may disagree with the experts' conclusions as to specificity, but that is fodder for cross-examination and not exclusion under *Daubert*.[28]

J&J offers nothing new. While there are different epithelial ovarian cancer subtypes, there are many commonalities including the etiology among them.[29] This

[27] *In re Johnson & Johnson*, 509 F. Supp. 3d at 181 (quoting J&J's briefing).

[28] *Id.*

[29] *See* Third Amended Rule 26 Expert Report of Judith Wolf, MD ("Wolf Amen. Rep.") at 3 ("Epithelial carcinoma of the ovary, fallopian tube, and peritoneum are usually considered as a single entity due to their common clinical behavior, risk factors, and pathogenesis.") (**Exhibit 7**); Third Amended Rule 26 Expert Report of Daniel L. Clarke-Pearson, MD ("Clarke-Pearson Am. Rep.") at 4 (**Exhibit 8)**; National Cancer Institute PDQ (*available at* https://www.cancer.gov/types/ovarian/hp/ovarian-epithelial-treatment-pdq#_1) (**Exhibit 9)**; American College of Obstetricians and Gynecologists (ACOG): Ovarian Cancer FAQs (attached as **Exhibit 10**); ACOG/Society of Gynecologic Oncologists (SGO) Practice Bulletin Hereditary Breast and Ovarian Cancer Syndrome (2017) ("Based on the contemporary understanding of the origins and management of ovarian cancer and for simplicity in this document, ovarian cancer also refers to fallopian tube cancer and primary peritoneal cancer.") (**Exhibit 11**).

is why much of the scientific evidence discusses epithelial ovarian cancer as a single disease, particularly with regard to causal factors such as inflammation.[30]

Nonetheless, to the extent relevant, the PSC's experts considered the different subtypes of epithelial ovarian cancer and formed their opinions accordingly.[31] The PSC's expert Dr. Levy explained:

> Q: Is your opinion related to all the different histologic types of epithelial ovarian cancer?
>
> A: My -- my opinion is not exclusive to any -- any one type. Certainly, the epithelial serous being the more common and most virulent type of cancers …From a mechanistic perspective, I mentioned some of the other subtypes and the common gene mutations that go along with them and as, again, supportive of the same mechanism. And I think, if anything, the -- the current data would suggest a -- a higher prevalence of a particular subtype of cancer but

[30] *See*, *e.g.*, Savant et al., "The Role of Inflammation and Inflammatory Mediators in the Development, Progression, Metastasis, and Chemoresistance of Epithelial Ovarian Cancer," *Cancers* 10, 251: 1-30., at p. 2 (2018) (discussing inflammation as a risk factor for all epithelial ovarian cancer subtypes) (**Exhibit 12**); Balkwill, F. and A. Mantovani, "Inflammation and cancer: back to Virchow?" *The Lancet* 357: 539-545, at p. 539 (2001) (identifying talcum powder as an "[i]nflammatory stimulus" for "ovarian" cancer) (**Exhibit 13**); Shan, W. and Jinsong Liu, "Inflammation: A hidden path to breaking the spell on ovarian cancer," *Cell Cycle* 8(19): 3107-3111, at p. 3108 (2009) (discussing epithelial ovarian cancer as single entity for purposes of inflammation) (**Exhibit 14**).

[31] *See* Clarke-Pearson Amen. Rep. at 4-6; Third Amended Expert Report of Anne McTiernan, MD, Ph.D. ("McTiernan Amen. Rep.") at 20 (**Exhibit 15**); Rule 26 Expert Report of Patricia G. Moorman ("Moorman Rep.") at 37 (**Exhibit 16**); Rule 26 Report of Ellen Blair Smith ("Smith Rep.") at 2-3 (**Exhibit 17**); Third Amended Expert Report of Jack Siemiatycki, MSc, PhD ("Siemiatycki Amen. Rep.") at 49-50 (**Exhibit 18**); Third Amended Rule 26 Expert Report of Judith Wolf, MD ("Wolf Amen. Rep.") at 3, 7, 8, 11 (Exhibit 7); Third Amended Expert Report of Rebecca Smith-Bindman, MD ("Smith-Bindman Amen. Rep.") at 3 (**Exhibit 19**).

> certainly not the -- the mechanism doesn't -- is not exclusive to any one type.[32]

Dr. Clarke-Pearson also recently explained that "most of the epidemiological studies have come down to say that talcum powder increases the risk of developing epithelial ovarian cancers," which is applicable to high-grade serous cancers as well clear cell and endometrioid cancers.[33]

J&J also again criticizes the use of ovarian epithelial cells in in vitro studies relied on by the PSC's experts. Mem. at 13-14. The medical literature supports the clinical relevance of molecules related to the cancer microenvironment in ovarian cancer stromal cells.[34] Normal immortalized ovarian epithelial cells are also relevant and frequently used for in vitro ovarian cancer studies.[35] The fact that these studies of human tissues demonstrated inflammation and genetic changes in human epithelial and fallopian cells is relevant.

---

[32] **Exhibit 20** (January 11, 2019, Deposition of Shawn Levy, Ph.D. ("Levy Dep.")) at 259:4-260:8; *see also id.* at 260:9-18.

[33] **Exhibit 21** (Deposition of Daniel Clarke-Pearson, M.D. ("Clarke-Pearson 2024 Dep.") at 370:21-371:25.

[34] Davidson et al., "The Role of the Tumor Stroma in Ovarian Cancer," *Front Oncol.* 4: 104 (2014) (**Exhibit 22**).

[35] Shin et al., "Establishment of five immortalized human ovarian surface epithelial cell lines via SV40 T antigen or HPV E6/E7 expression," *PLOS One* 13(10): 1-16, at p. 1 (2018) (immortalized "human ovarian surface epithelial (HOSE) cells are a critical cell source for ovarian cancer research.") (**Exhibit 23**).

B. THE PSC'S EXPERTS' OPINIONS ON MIGRATION ARE SUPPORTED BY RELIABLE SCIENTIFIC AND MEDICAL LITERATURE

J&J also reasserts its arguments on migration, contending that Judge Wolfson applied the wrong Rule 702 standard in finding these opinions reliable because none of the studies involved externally applied talcum powder. As explained above, Judge Wolfson applied the correct preponderance of evidence standard in finding that the PSC's experts' migration opinions are reliable and admissible.[36] J&J's arguments concerning specific studies go to weight and not admissibility.

1. The PSC's Experts' Migration Opinions Are Supported by Reliable Human Evidence

J&J does not contend that the migration studies upon which the PSC's expert rely are unreliable. Instead, J&J argues that migration is not supported by the numerous human migration studies because those studies all "involved material inserted deep into the internal reproductive tract" (rather than perineal application), manipulation of the environment to encourage migration (rather than normal human behavior), and particles other than talc.

Once again, these criticisms go to the weight of the evidence, not admissibility. The PSC's experts are not required to point to a study specifically showing the migration of talc particles from the perineum to the fallopian tubes and

[36] *In re Johnson & Johnson*, 509 F. Supp. 3d at 174-175.

ovaries to conclude that migration is plausible.[37] Thus, J&J's critiques of the evidence are misplaced.

First, migration of talc and asbestos particles from the perineum to the fallopian tubes and ovaries is a widely accepted route of exposure. The FDA states that the "potential for particulates to migrate from the perineum and vagina to the peritoneal cavity is indisputable."[38] IARC states: "Consumer products (e.g. cosmetics, pharmaceuticals) are the primary sources of exposure to talc for the general population. Inhalation and dermal contact (i.e. through perineal application of talcum powder) are the primary routes of exposure."[39] Health Canada also recently stated "the available animal and human studies…clearly indicate that particles, including talc, may transfer from the vagina to the fallopian tubes and ovaries following perineal application."[40]

Second, J&J completely ignores real life and female anatomy. Access to the vagina from the perineum does not require the moving of mountains that J&J

---

[37] *Milward*, 639 F.3d at 23; *In re Testosterone Replacement Therapy Prod. Liab. Litig. Coordinated Pretrial Proceedings*, No. 14 C 1748, 2017 U.S. Dist. LEXIS 69399, *1005 (N.D. Ill. May 8, 2017) (admitting expert testimony where there was no "single piece of evidence the experts rely upon [that] is sufficient to support their causation opinions. But the experts have adequately explained why they have reached their conclusions on the basis of the evidence as a whole.").

[38] April 1, 2014, FDA Response to Citizen's Petition (as **Exhibit 24**).

[39] IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, "Arsenic, Metals, Fibres, and Dusts Volume 100 C A Review of Human Carcinogens," (2012) at 232 (hereinafter, "IARC 2012") (relevant portions attached as **Exhibit 25**).

[40] Health Canada, Screening Assessment Talc, at p. 34, Exhibit 1.

suggests.[41] Among other things, women exercise, use the restroom, use tampons, lay down, and engage in sexual intercourse – all activities that can result in talcum powder that was applied to their perineum migrating or translocating into their vaginas.[42] J&J's own gynecologic oncologist expert Dr. Cheryl Saenz conceded that talcum powder placed on the perineum could be moved into the vagina through ordinary activities such as intercourse and tampon use.[43]

For this reason, J&J's experts, the PSC's experts, regulatory authorities, and the medical and scientific community all agree that there is a pathway from the outside world to the peritoneal cavity through the vagina, uterus and fallopian tubes.[44] Therefore, studies that show migration from the vagina upward are relevant

---

[41] *See* January 19, 2019, Deposition of Arch Carson ("Carson Dep.") at 301:16-302:2 (testifying that application to the perineum is equivalent to materials instilled into the vagina") (**Exhibit 26**).

[42] January 7, 2019, Deposition of Dr. Judith Wolf ("Wolf Dep."), at 194:7-195:20 (**Exhibit 27**); Huncharek et al., "Use of cosmetic talc on contraceptive diaphragms and risk of ovarian cancer: a meta-analysis of nine observational studies," *Euro. J. of Cancer Prev.* 16(5): 422-429, at p. 423 (2007) (recognizing that "in the experimental setting translocation of talc particles to the human ovary can occur with deliberate or inadvertent manipulations of patients in the supine position") (**Exhibit 28**); Heller et al., "Asbestos Exposure and Ovarian Fiber Burden," *Am. J. of Indust. Med.* 29: 435-439, at p. 438 (1996) (proposing sexual intercourse as a "transporting vector for asbestos fibers" to the ovaries) (**Exhibit 29**).

[43] **Exhibit 30** (Saenz 6/19/24 Dep.) at 290:15-291:17; *see also* March 27, 2019, Deposition of Kevin Holcomb M.D. ("Holcomb 2019 Dep.") at 421:23-422:12 ("[I]f you're saying is it possible, I'd have to say yes.") (**Exhibit 31**); March 13, 2019 Deposition of Cheryl Saenz, M.D. ("Saenz 2019 Dep.") at 209:7-14 ("I do think that in terms of biologic plausibility, there is some data that there can be particulate matter that can make it to the ovaries, but I don't actually know one way or another if talc can do that.") (**Exhibit 32**).

[44] Clarke-Pearson Amen. Rep. at 12; Wolf Amen. Rep. at 13; April 2014 FDA Letter; IARC 2012 at 232, Ex. 25; Health Canada, Screening Assessment Talc, at p. 34; Folkins, A., Elke A Jarboe, Jonathan L. Hecht, Michael G. Muto, and Christopher P. Crum, "Assessing Pelvic Epithelial Cancer Risk and Intercepting Early Malignancy," *Diagnostic Gynecologic and Obstetric Pathology*, at p. 846 (3d Ed. 2017) ("Talc placed on the perineum may enter the vagina and ascend

to whether powder placed on the perineum could similarly migrate once it gets in the vagina.

Third, the evidence is overwhelming that once in the vagina, particles rapidly migrate upward to the ovaries and fallopian tubes. Uterine peristalsis (the regular and natural contractions that occur in the genital tract) creates contractions that result in upward migration of particles from the vagina to the ovaries and fallopian tubes.[45] Judge Wolfson found the PSC's opinions concerning peristalsis reliable.[46] Peristalsis has been observed to occur at a rate of 1.2-2.8 contractions per minute, depending

---

to the upper genital tract.") (**Exhibit 33**); Houghton et al., "Perineal Powder Use and Risk of Ovarian Cancer," *JNCI* 106: 1-6, at p. 1 (2014) ("Talc particulates from perineal application have been shown to migrate to the ovaries.") (**Exhibit 34**); Langseth et al., "Perineal use of talc and risk of ovarian cancer," *J. Epidemiol. Comm. Health* 62: 358-360, at p. 358 (2008) ("A majority of women experience retrograde menstruation; this suggests a mechanism by which talc can travel through the female production tract to the ovaries.") (**Exhibit 35**); Henderson et al. (1986), "The Demonstration of the Migration of Talc from the Vagina and Posterior Uterus to the Ovary in the Rat," *Env. Res.* 40: 247-250, at p. 247 ("Direct communication between the external environment and the peritoneal cavity exists in the female via her genital tract.") (**Exhibit 36**).

[45] Jones, Richard E. and Kristen H. Lopez, "Human Reproductive Biology," at 162 (4th Ed. 2006) ("[D]ead sperm reach the oviduct at about the same time as do live sperm. Thus, sperm tail beating probably is not important during sperm transport through the uterus, so it must be the muscle contraction and movement of cilia in the female reproductive tract that facilitate sperm transport.") (**Exhibit 37**); Kissler et al., "Uterine contractility and directed sperm transport assessed by hysterosalpingoscintigraphy (HSSG) and intrauterine pressure (IUP) measurement," *Acta Obstet Gynecol Scand* 83: 369-374, 369-70 (2004) (recognizing that contractions occur through a woman's cycle) (**Exhibit 38**); Kunz et al., "The Uterine Peristaltic Pump Normal and Impeded Sperm Transport within the Female Genital Tract," *The Fate of the Male Germ Cell* 49: 267-277, at p. 269 (1997) ("Since the velocity of sperm movement does not itself account for covering such a long distance through the female genital tract within a few minutes, rapid sperm transport is considered a passive phenomenon and has been ascribed to uterine contractions.") (**Exhibit 39**); Zervomanolakis et al., "Physiology of Upward Transport in the Human Female Genital Tract," *Ann. N.Y. Acad. Sci.* 1101: 1-20, at p. 1 (2007) (discussing uterus and fallopian tubes as "functionally united peristaltic pump") (**Exhibit 40**).

[46] *In re Johnson & Johnson*, 509 F. Supp. 3d at 173-175. Indeed, J&J's own gynecologic oncologist expert Dr. Holcomb concedes genital peristalsis exists. Holcomb 2019 Dep. at 437:23-438:11.

on the phase of a woman's cycle.[47] Additionally, retrograde menstruation – the upward movement of menstrual blood through the fallopian tubes – is well-documented and occurs in up to 90% of women.[48]

It is not surprising then, that upward migration of particulates through the female genital tract occurs. In Sjosten et al. ((2004), the study subjects received a "routine gynecological examination" by a doctor using cornstarch powdered gloves.[49] "Any medication that might have influenced the tubal patency [opening the fallopian tubes]" was not administered.[50] No other steps were taken to influence migration.[51] Yet, within 24 hours and for up to 4 days following examination, cornstarch was found in the cervical canal, uterine cavity, and fallopian tubes.[52] The

[47] Kunz et al. (1997) at p. 269; Henderson et al., at p. 247 (1986) ("The rhythmic muscular contractions of the uterus that occur spontaneously and the illicit currents established by the epithelial cells of the genital tract may contribute to the translocation process.") (Exhibit 36).

[48] Halme et al., "Retrograde Menstruation in Healthy Women and in Patients with Endometriosis," *Obst. & Gyn.* 64: 151-154, at p. 153 (1984) (observing retrograde menstruation in 90% of study patients and concluding that "the fallopian tubes play an important role as conduits for menstrual blood") (**Exhibit 41**); Blumenkrantz et al., "Retrograde Menstruation in Women Undergoing Chronic Peritoneal Dialysis," *Obstetrics & Gynecology* 57(5): 667-670, at p. 669 (1981) ("[R]etrograde bleeding regularly occurs with menstruation in most if not all women on peritoneal dialysis and quite possibly in most menstruating women in the general population.") (**Exhibit 42**); *see also* Wolf Amen. Rep. at 14 (Exhibit 7); Smith Dep. at 318:13-319:6 ("a majority of women experience retrograde menstruation") (**Exhibit 43**).

[49] Sjosten et al. "Retrograde Migration of Glove Powder in the Human Female Genital Tract", *Human Reprod* 19(4): 991-995 (2004), at p. 992 (**Exhibit 44**).

[50] *Id.*

[51] That the women in this study were laying down is not atypical of what women do in their daily lives. *See* Mem. at 18.

[52] Sjosten et al. (2004), at pp. 992-93, 995.

study authors concluded that "[s]ince evidence suggests that a retrograde migration could be a general mechanism…we should be critical of harmful substances, e.g. glove powder, that could migrate from the vagina to abdominal cavity."[53]

Similarly, particulate radioactive material was observed in the ovaries and fallopian tubes of 14 of 21 study patients within 24 hours after being placed in the vagina.[54] The study authors noted that "[i]f transit can take place so easily, it is probably the same for many chemical substances used for hygienic, cosmetic, or medicinal purposes, many of which may have potential carcinogenic or irritating properties."[55]

Carbon particles also were observed in the fallopian tubes of two of three patients within 28 and 34 minutes, respectively, after being placed in the posterior fornix.[56] The study authors concluded that the data confirm that "[c]ontractions of

---

[53] *Id.* at p. 995.

[54] Venter and Iturralde, "Migration of a Particulate Radioactive Tracer from the Vagina to the Peritoneal Cavity and Ovaries," *S. Afr. Medi. J.* 55: 917-919, at pp. 918, 919 (1979) (**Exhibit 45**). The radioactive material was placed in the vagina with the patient laying on her back with her buttocks slightly elevated and her legs closed; the patient remained in this position for two hours. *Id.* at pp. 917-918.

[55] *Id.* at p. 919; *see also* Iturralde and Venter, "Hysterosalpingo-Radionuclide Scintigraphy (HERS)," *Sem. in Nuc. Med.* 11(4): 301-314, at pg. 301 (1981) ("Access of talc to the peritoneal cavity is most likely through the vagina.") (**Exhibit 46**); Zervomanolakis et al. (2007) at pp. 6-7 (labeled particles were detected in the uterine cavity within two minutes of placement in vagina and "[u]ptake into the uterus" of all patients, and in one or both fallopian tubes of 79% of patients) (Exhibit 40).

[56] Egli and Newton, "The Transport of Carbon Particles in the Human Female Reproductive Tract," *Fert. & Ster.* 12: 151-155, at p. 153 (1961) (**Exhibit 47**). The carbon particles were suspended in dextran and placed at the posterior fornix as the women laid downward at a 15° angle and were given oxytocin to aid in contractions. *Id.* at p. 152. Upward migration resulted. *Id.* at 153.

the muscle of the uterus or other reproductive organs" encourage upward migration of sperm and other particulates.[57]

Although these studies did not specifically look at whether particulates applied to the perineum (as opposed to the vagina) can migrate to the ovaries or fallopian tubes, they are highly relevant and instructive because it is universally accepted in the medical and scientific literature that "[t]alc placed on the perineum may enter the vagina and ascend to the upper genital tract."[58] That is because normal activities such as walking, vaginal intercourse, use of tampons, going to the bathroom, and exercise, can easily move particulates from the perineum to the

[57] *Id.* at 154.

[58] Folkins, et al., at p. 846 (3d Ed. 2017), Ex. 33; *see also* Health Canada, Screening Assessment Talc, at p. 34 ("[T]he available animal and human studies…clearly indicate that particles, including talc, may transfer from the vagina to the fallopian tubes and ovaries following perineal application."), Ex. 1; Schildkraut et al., "Association between Body Powder Use and Ovarian Cancer: The African American Cancer Epidemiology Study (AACES)," *Cancer Epidemiol. Biomarkers Prev.* 25: 1411-1417, at p. 1415 (2016) ("As most high-grade serous EOC, but not nonserous subtypes, arise in the fallopian tube, it is possible that direct exposure through the genital tract specifically effects this disease subtype.") (**Exhibit 48**); Houghton et al., at p. 1 (2014) ("Talc particulates from perineal application have been shown to migrate to the ovaries.") (Ex. 34); Langseth et al., "Perineal use of talc and risk of ovarian cancer," *J. Epidemiol. Comm. Health* 62: 358-360, at p. 358 (2008) ("A majority of women experience retrograde menstruation; this suggests a mechanism by which talc can travel through the female production tract to the ovaries.") (Ex. 35); Henderson et al. (1986), at p. 247 ("Direct communication between the external environment and the peritoneal cavity exists in the female via her genital tract.") (Exhibit 36); Merritt et al., "Talcum powder, chronic pelvic inflammation and NSAIDs in relation to risk of epithelial ovarian cancer," *Int. J. Cancer*, 122: 170-176, at p. 174 (2008) ("[I]t has been demonstrated experimentally that talc particles can reach the ovaries in humans and rodents as the result of talc use in the pelvic region….") (**Exhibit 49**); *See also* Clarke-Pearson Amen. Rep. at 12, Exhibit 8; Wolf Amen, Rep. at 13-15, Exhibit 7.

vagina.[59] In addition, the particles studied in the migration literature are similar in size and other chemical and morphologic features to those found in talcum powder products.[60]

Finally, while the PSC's experts readily acknowledge the differences among the types of particulates used in the studies,[61] the type of particle does not appear to matter as all different types of particles (including cornstarch) behave the same by migrating upward.

2. The Animal Studies Provide Additional Support for Biological Plausibility

J&J also critiques the PSC's experts' reliance on animal studies.[62] Animal studies may be relied upon for purposes of biological plausibility.[63] Here, the PSC's

[59] Wolf Dep. at 194:7-195:20, Exhibit 27; Huncharek et al., at p. 423 (2007) (recognizing that "in the experimental setting translocation of talc particles to the human ovary can occur with deliberate or inadvertent manipulations of patients in the supine position") (Exhibit 28); Heller et al., at p. 438 (1996) (proposing sexual intercourse as a "transporting vector for asbestos fibers" to the ovaries) (Exhibit 29).

[60] Health Canada, Screening Assessment Talc, at p. 19, Exhibit 1 (recognizing that the particles studied in Egli et al. (1961) and Venter and Iturralde (1979) are "similar in size to talc.").

[61] *See* Wolf Amend. Rep. at 13-14; Smith-Bindman Amen. Rep. at 33, Exhibit 19; Smith Rep. at 16, Exhibit 43; Clarke-Pearson Amen. Rep. at 12; McTiernan Amen. Rep. at 88-89, Exhibit 15.

[62] Mem. at 19.

[63] *In re Testosterone Replacement Therapy*, 2017 U.S. Dist. LEXIS 69399, at *1015; *In re Actos (Pioglitazone Prods. Liab. Litig.*, No. 12-CV-00064, 2013 U.S. Dist. LEXIS 179235, at *12 (W.D. La. Dec. 19, 2013) (approving reliance on animal studies to show biological plausibility); *Smith v. I-Flow Corp.*, No. 09 C 3908, 2011 U.S. Dist. LEXIS 47197, *2 (N.D. Ill. May 3, 2011) (admitting expert opinion that relied in part on in vitro and animal studies).

experts rely on the extensive *human data* on migration discussed above, not on the handful of animal studies.[64]

While J&J critiques the use of animal data for purposes of opining on migration in humans, it also falsely accuses the PSC's experts of "cherry-picking" for failing to consider a *single* animal study that J&J likes – Wehner et al. (1986).[65] The PSC's experts did consider Wehner (1986) with the totality of the evidence.[66]

Wehner (1986) does not disprove migration. The authors there simply concluded that based upon the limited study, "[i]t is less clear whether or not inanimate particles such as carbon black or talc can translocate of their own accord from the vagina to the oviducts and beyond."[67] Importantly, Wehner predated the majority of studies relied on by the PSC's experts, including Sjosten et al. (2004), which found that cornstarch (which is similar to talc) migrates in humans from the

[64] *See* Clarke-Pearson Amen. Rep. at 12, Ex. 8; Smith Rep. at 16-17, Ex. 17; McTiernan Amen. Rep. at 88-89, Ex. 15; Moorman Rep. at 33, Ex. 16; Third Amended Expert Report of Laura M. Plunkett, Ph.D., DABT ("Plunkett Amen. Rep.") at 30-31 (**Exhibit 50**); Expert Report of Arch Carson, MD, Ph.D. at 6 (**Exhibit 51**); Siemiatycki Amen. Rep. at 74, Ex. 18; Expert Report of Sonal Singh, MD, MPH ("Singh Rep.") at 18-19, 57 (**Exhibit 52**); Smith-Bindman Amen. Rep. at 32-33, Ex. 19.

[65] Mem. at 20 (citing Wehner et al., "On Talc Translocation From the Vagina to the Oviducts and Beyond," *Food Chem Toxicol* 24: 329-338 (1986)). Notably, Wehner et. al. (1986) was a study funded by PCPC (formerly known as the Cosmetic, Toiletry and Fragrance Association (CTFA), of which J&J is a member. *See* Wehner et al. (1986) at p. 329. J&J also funded other studies conducted by Wehner.

[66] Plunkett Amen. Rep. at 35-37; Singh Rep. at 57.

[67] Wehner et al. (1986) at p. 331.

vagina to the ovaries and fallopian tubes.[68] Additionally, Wehner assumed that the behavior of particles would be governed by the "laws of physics" that would not permit particles to migrate "upstream." This statement was pure speculation at the time and has since been disproven by the discovery of the uterine "peristaltic pump."

Rather than rely on a single animal study as J&J does, the PSC's experts rely on numerous human migration studies discussed above, conclusions by IARC, Health Canada, and the FDA, and medical textbooks. J&J's baseless criticism that the PSC's experts failed to consider one study (even though they did consider it) is not a basis for exclusion of their opinions. As Judge Wolfson already found, the PSC's experts' migration opinions are well-supported by reliable evidence and are admissible.

3. The Presence of Talc and Asbestos in Reproductive Tissue Supports Migration

Pathological studies also confirm the presence of talc and asbestos (constituents of talcum powder) in human ovarian cells and lymph nodes, further supporting the opinion that particulates such as talcum powder can and do migrate within the human body.[69]

---

[68] Sjosten et al. (2004) at p. 992-93, 995, Ex. 44.

[69] Gertig et al., "Prospective Study of Talc Use and Ovarian Cancer," *J. of the Nat'l Cancer Inst.* 92(3): 249-252, at p. 252 (2000) ("Talc is able to migrate through the genital tract and gain access to the ovaries because talc fibers have been detected in benign and malignant ovarian tissue, although no relation between reported levels of talc exposure and ovarian talc counts has been observed.") (**Exhibit 53**); Cramer et al., "Genital Talc Exposure and Risk of Ovarian Cancer," *Int. J. Cancer* 81: 351-356, at p. 356 (1999) ("It has been demonstrated that inert particles

In Henderson et al. 1971, talc particles were found "deep within" or "embedded" in the human tissue samples from 10 out of 13 ovarian tumors, 12 out of 21 cervical tumors, and 5 out of 21 normal ovaries.[70]

In two separate studies by Heller et al. in 1996, talc was identified in human ovarian tissue samples of women who reported perineal talcum powder use[71] and asbestos was identified in nine of 11 women that were exposed to asbestos.[72] The authors concluded that "[t]he detection of talc in all the ovaries demonstrates that talc can reach the upper genital tract"[73] from perineal use and that "women with a positive exposure history had asbestos detected in their ovaries more frequently."[74]

---

contaminating the vagina can reach the ovaries [and] [t]alc has been found in both normal and malignant ovarian tissue.") (**Exhibit 54**); Langseth et al. (2008) at p. 358 ("From pathological studies it is known that particles and fibres that enter the body can migrate to distant organs."); Siemiatycki Amen. Rep. at 74, Ex. 18; Moorman Rep. at 33, Ex. 16; Smith-Bindman Amen. Rep. at 33, Ex. 19; Plunkett Amen. Rep. at 31, Ex. 50; Wolf Amen. Rep. at 14, Ex. 7; Clarke-Pearson Amen. Rep. at 12, Ex. 8; Singh Rep. at 57, Ex. 52.

[70] Henderson et al., "Talc and Carcinoma of the Ovary and Cervix," *The Journal of Obstetrics and Gynaecology* 78: 266-272, at pp. 266-268 (1971) (**Exhibit 55**).

[71] Heller et al., "The relationship between perineal cosmetic talc usage and ovarian talc particle burden," *Am. J. Obstet. Gynecol.* 174: 1507-1510, at p. 1509 (1996) (**Exhibit 56**); Wolf Amen. Rep. at 14; Clarke-Pearson Amen. Rep. at 12; McTiernan Amen. Rep. at 88, Ex. 15; Moorman Rep. at 33, Ex. 16; Siemiatycki Amen. Rep. at 74; Plunkett Amen. Rep. at 30; Singh Rep. at 57; Rule 26 Expert Report of Sarah Kane, M.D. ("Kane Rep.") at 14 (**Exhibit 57**).

[72] Heller et al. (1996–asbestos), at p. 437 (Exhibit 29); *see also* Mostafa et al., "Foreign Body Granulomas in Normal Ovaries," *Obstetrics and Gynecology* 66: 701-702, at p. (1985) (of all women operated on at Johns Hopkins Hospital for pelvic disease, 9% had magnesium silicate (commonly found in talc and asbestos) granulomas in their ovaries and another 9% had "histologic entities that were very similar") (**Exhibit 58**).

[73] Heller et al. (1996-talc) at pp. 1509-1510, Ex. 56.

[74] Heller et al. (1996-asbestos) at p. 439 Ex. 29.

Talc particles also have been found in human pelvic lymph nodes of women that used talcum powder on their genitals. Cramer et al. 2007 identified talc in three of four lymph nodes of a women who reported using talcum powder in her genital area daily for 30 years.[75] McDonald et al. 2019a examined pelvic lymph nodes of users and non-users of genital talcum powder and found "the level of talc in nodal tissue at least five times higher in those who used talc genitally compared to those who had not," confirming "earlier observations that talc particles, from perineal exposure, can and do migrate to pelvic lymph nodes."[76] McDonald et al. 2019b found talc in multiple pelvic organ sites of ovarian cancer patients who had known perineal exposure to talcum powder.[77]

And, most recently, in Johnson et al. 2020, talc particles and fibers found in pelvic tissue of ovarian cancer patients who had used talcum powder products were shown to be similar in size and shape to those found in J&J's baby powder.[78]

---

[75] Cramer et al., "Presence of Talc in Pelvic Lymph Nodes of a Woman with Ovarian Cancer and Long-Term Genital Exposure to Cosmetic Talc," *Obstetrics & Gynecology* 110: 498-501, at p. 499 (2007) (**Exhibit 59**); *see also* Smith-Bindman Amen. Rep. at 33, Ex. 19; Kane Rep. at 14; McTiernan Amen. Rep. at 89, Ex. 15; Moorman Rep. at 33.

[76] McDonald et al., "Correlative polarizing light and scanning electron microscopy for the assessment of talc in pelvic region lymph nodes," *Ultrastructural Pathology* 43: 13-27, at pp. 21, 24 (2019) ("McDonald 2019a") (**Exhibit 60**).

[77] McDonald et al., "Migration of Talc From the Perineum to Multiple Pelvic Organ Sites," *Am. J. Clin. Pathol.*152: 590-607, at p. 598 (2019) ("McDonald 2019b") (**Exhibit 61**).

[78] Johnson KE et al., "Analytic comparison of talc in commercially available baby powder and in pelvic tissues resected from ovarian carcinoma patients." *Gynecol Oncol* 159: 527-533 (2020) (**Exhibit 62**).

The migration literature together with the presence of talc and asbestos in ovarian tissue and lymph nodes sufficiently supports the migration of talcum powder within the genital tract. As Johnson et al. (2020) concludes, the similarity between particles found in ovarian tissue of cancer patients and J&J's talcum powder, "combined with previous epidemiological literature and tissue-based analytical studies, provides further evidence that the small, isodiametric particles that dominate in commercial talc containing baby powder can migrate from the perineum and become lodged in distal structures in the female reproductive tract…."[79]

Focusing on Henderson (1971), Heller (1996-talc), McDonald (2019), and Johnson (2020), J&J argues that the existence of talc particles in ovaries does not prove that it got there through perineal talcum powder use. While J&J may be correct that in isolation, these studies only prove that talc got to the ovaries and lymph nodes from somewhere, the studies are not reviewed in isolation. Rather, when viewed in the context of the totality of the evidence on the ability of particles to migrate upward from the vagina to the ovaries and fallopian tubes and through inhalation, the presence of talc in the ovaries and lymph nodes has clinical and scientific significance.

J&J also suggests that the talc could have come from contamination or that the authors of these studies were biased. But J&J has no basis in fact for attributing

[79] *Id.* at p. 527.

the presence of talc in ovarian tissue solely to contamination or bias. The study authors expressly controlled for contamination and noted that the talc was deeply embedded in the tissue, indicating it was not from contamination.[80] Even Wehner, the same researcher that J&J touts, concluded that contamination could be ruled out when talc particles are found in the ovaries: "Talc particles found, for example, *on* ovarian tissue might be contaminants deposited during sample collection and processing. For talc particles *in* the ovarian tissue, contamination during sample collection and processing can be ruled out."[81]

Additionally, McDonald (2019a), which was expressly designed to account for contamination, found talc in ovarian tissue and confirmed the "earlier observations that talc particles, from perineal exposure, can and do migrate to pelvic

[80] Heller et al. (1996-talc) at p. 1508 ("Routinely, all solutions are checked for detectable limits of contaminating particles; all places where particles could have contaminated the specimen, such as paraffin, are also controlled for.") Ex. 56; Henderson et al. (1971) at p. 268, Ex. 55; McDonald et al. (2019b) at p. 592, Ex. 61 (discussing procedures taken to eliminate contamination); Johnson et al. (2020) at p. 528, Ex. 62 ("As a precaution against contamination, the blocks were handled with particle-free gloves on precleaned surfaces and were sectioned…This removed surface contamination from previous handling. The blocks were always kept in closed containers to prevent any laboratory contamination.").

[81] Wehner et al., "Biological effects of cosmetic talc," *Fd Chem. Toxic* 32(12): 1173-1184, at p. 1175 (1994) (attached as **Exhibit 63**). McDonald et al. (2019b) did not conclude that the Heller 1996 results "likely resulted from laboratory contamination." Mem. at 23. Rather, the authors simply acknowledged that contamination "could have also played a role." McDonald et al. (2019b) at p. 591, Ex. 61. As a result, the authors took significant steps to eliminate contamination and still found talc in multiple organ sites. *Id.* at pp. 592, 598.

lymph nodes."[82] These studies are reliable and when properly considered in the context of the totality of the evidence, support the PSC's experts' opinions.

4. The Scientific and Medical Literature Supports Inhalation as a Secondary Mechanism

Not surprisingly, J&J argues that Judge Wolfson's exclusion of inhalation is the only area of biological plausibility she got correct. Notably, Judge Wolfson did not apply a different legal standard to inhalation. She simply found that the evidence previously relied on by the PSC's experts was not sufficient because it did not explain how inhaled talc "moves through the lymphatic system to the ovaries."[83]

The evidence supporting inhalation as a possible mechanism has only strengthened. Health Canada recently conducted an extensive review of the scientific evidence on inhalation of talc and concluded, "Considering available lines of evidence, critical health effects have been identified following inhalation exposure to respirable talc particles."[84] Health Canada found that McDonald et al. (2019a), "supports the hypothesis of the migration of talc from the perineal region through lymphatic pathways by demonstrating the presence of talc in multiple pelvic tissues and lymph nodes simultaneously."[85]

---

[82] McDonald et. al (2019a) at p. 24, Ex. 60.

[83] *In re Johnson & Johnson*, 509 F. Supp. 3d at 176.

[84] Health Canada, Screening Assessment Talc, at p. 41, Ex. 1.

[85] *Id.* at p. 21.

Additionally, Steffen et al. (2020) conducted an asbestos exposure assessment during use of cosmetic talc products and "found that cosmetic talc users can be exposed to 2.57 f/cc asbestos in the breathing zone during perineal talc application."[86] The authors also identified asbestos fibers in pelvic tissue, including pelvic lymph nodes, and concluded that "[t]hese cases provide more evidence of the causal link between asbestos, talc, and ovarian cancer and indicate that asbestos is present in consumer talc products at levels sufficient to cause disease."[87]

IARC concluded that all forms of asbestos (which is present in talcum powder) are Group 1 carcinogens and cause ovarian cancer through inhalation.[88] Additionally, IARC acknowledges that inhaled fibers (asbestos and others) travel to other parts of the body including the lymphatic system.[89]

J&J ignores the totality of the evidence and once again focuses on individual study, arguing that Cramer (2007), which found talc in lymph nodes, does not explain how talc got there. However, additional studies also finding talc and asbestos

---

[86] Steffen et al., "Serous Ovarian Cancer Caused by Exposure to Asbestos and Fibrous Talc in Cosmetic Talc Powders – A Case Series," *JOEM* 62:65-77 (2020) (**Exhibit 64**).

[87] *Id.*

[88] IARC 2012 at pp. 219, 232, 256, 280, Ex. 25.

[89] IARC 2012 at p. 280, Ex. 25 ("The route of translocation of asbestos fibres from the lungs to distant sites is unknown, although lymphatic translocation of amosite fibres deposited in the lungs has been shown in experimental animals."); *see also* Cramer et al. 2007 (talc found in lymph nodes).

in the lymph nodes of talcum powder users support the hypothesis that inhaled talcum powder can enter the lymphatic system.[90]

J&J also again argues that if inhalation is a secondary mechanism, other cancers should be associated with talcum powder use.[91] However, different tissues react differently to carcinogens.[92] While it is entirely possible that talcum powder products can cause an increased risk of other cancers, the PSC's experts were not tasked with making that scientific determination. Nor is that required for purposes of biological plausibility. The PSC's experts' opinions on inhalation as a secondary mechanism are reliable and admissible.

C. THE SCIENTIFIC LITERATURE SUPPORTS CHRONIC INFLAMMATION FROM TALCUM POWDER PRODUCTS AS A CAUSE OF OVARIAN CANCER

J&J also reasserts its same arguments about inflammation, ignoring the totality of the evidence and the correct standard of biological plausibility. J&J argues that a handful of individual studies support its position that talc does not cause chronic inflammation. This is not a basis for exclusion under *Daubert*. The PSC's experts' opinions on chronic inflammation are reliable and overwhelmingly well supported by the totality of the literature. To the extent J&J disagrees with the weight

[90] Health Canada, Screening Assessment Talc, at p. 18, Ex. 1 (discussing McDonald et al. (2019b)); *see also* Steffen et al. (2020), Ex. 64.

[91] Mem. at 26.

[92] *See* Clarke-Pearson 2019 Dep. at 210:24-212:10, **Exhibit 65**.

of a particular study or believes it has evidence to support its position, those are matters for cross-examination before a jury, not exclusion under *Daubert*.[93]

1. The Scientific Evidence Supports Talcum Powder Causes Chronic Inflammation

Numerous peer-reviewed studies have concluded that talcum powder causes an inflammatory response that increases the risk of ovarian cancer.[94] As Gates et al. (2008) explained: "Normal ovarian cells treated with talc are more likely to undergo cell proliferation and neoplastic transformation, and cellular generation of reactive oxygen species increases with increasing exposure to talc."[95] Similarly, Health

[93] *Daubert*, 509 U.S. at 596; *In re TMI Litigation*, 193 F.3d at 664, 665.

[94] *See*, *e.g.*, Penninkilampi, et al. "Perineal Talc Use and Ovarian Cancer. A Systematic Review and Meta-Analysis." *Epidemiology* 29(1): 41-49, at p. 45 (2018) ("If chronic inflammation due to ascending foreign bodies is indeed the mechanism by which talc is associated with increased ovarian cancer, then these results fit the picture.") (**Exhibit 66**); Mills et al., "Perineal talc exposure and epithelial ovarian cancer risk in the Central Valley of California," *Int'l J. Cancer* 112(3): 458-464, at p. 458 (2004) ("Collectively, these studies point to a possible etiologic role of talc in ovarian cancer via an inflammatory process at the site of the ovarian epithelium.") (**Exhibit 67**); Wu et al., "Markers of inflammation and risk of ovarian cancer in Los Angeles County," *Int. J. Cancer* 124: 1409-1415, at p. 1414 (2009) ("Our findings on talc and endometriosis are consistent with previous findings and are compatible with the hypothesis that these factors increase the risk of ovarian and that inflammation may be a common pathway.") (**Exhibit 68**) ; Merritt et al. (2008), at p. 170, Ex. 49 ("Indeed the most consistent evidence linking inflammation with ovarian cancer comes from the many reports that use of talc in the perineal region increases ovarian cancer risk."); Taher et al., "Systematic Review and Meta-Analysis of the Association between Perineal Use of Talc and Risk of Ovarian Cancer," *unpublished* at p. 26 (2018) ("Chronic inflammatory response and alteration in local immunogenicity are possible mechanisms" for talcum powder causing ovarian cancer") (**Exhibit 69**).

[95] Gates et al., "Talc use, variants of the GSTM1, GSTT1, and NAT2 genes and risk of epithelial ovarian cancer," *Cancer Epidemiol Biomarkers Prev.* 17(9): 2436-2444, at p. 2443 (2008) (**Exhibit 70**).

Canada concluded, "[t]here is support for an association of inflammation and increased risk of ovarian cancer."[96]

Balkwill, a world-renowned cancer researcher identified talcum powder use as an inflammatory stimulus related to ovarian cancer in 2001.[97] Although J&J claims this study is "outdated,"[98] a citation search on Google Scholar reveals that the article has been cited over 2600 times since 2020, providing solid evidence that it is certainly not considered outdated by the scientific community. Moreover, numerous researchers subsequently have opined that talcum powder is an inflammatory mediator that contributes to ovarian cancer.[99]

The science supports these conclusions. *First*, the link between chronic inflammation and ovarian cancer is well-supported.[100] "[D]espite being a designed

---

[96] Health Canada, Screening Assessment Talc, at p. 20, Ex. 1 ("With respect to talc and induction of tumours, local chronic irritation leading to an inflammatory response is one possible mechanism of tumour progression that is frequently hypothesized in the literature…[T]here is support for an association of inflammation and increased risk of ovarian cancer.").

[97] Balkwill and Mantovi (2001), at p. 539, Table 1 (identifying "[p]elvic inflammatory disease/***talc***/tissue remodeling" as "[i]nflammatory stimulus" that are associated with ovarian cancer) (emphasis added) Ex. 13.

[98] Mem. at 37.

[99] *See supra* n.95.

[100] *See*, *e.g.*, Balkwill, F. and A. Mantovani (2001) at p. 539 (recognizing that as far back as 1863, inflammatory cells (leukocytes) were identified in tumor tissue); *id.* ("increased risk of malignancy is associated with the chronic inflammation caused by chemical and physical agents") Ex. 13; Coussens, L. and Zena Werb, "Inflammation and Cancer," *Nature* 420: 860-867, at Table 1 (2002) (listing "[p]elvic inflammatory disease, chronic cervicitis" as pathological conditions associated with "[o]varian carcinoma, cervical/anal carcinoma") (**Exhibit 71**); Okada, F., "Beyond foreign-body induced carcinogenesis: Impact of reactive oxygen species derived from inflammatory cells in tumorigenic conversion and tumor progressions," *Int. J. Cancer* 121: 2364-2372, at p. 2364 (2007) ("[T]umor development and progression are accelerated inevitably by inflammation caused

response to eliminate pathogens and other agents harmful to the host, inflammation when deregulated or inappropriately maintained has the potential to cause injury, necrosis, and malignant transformation."[101] "Chronic inflammation is induced by biological, chemical, and physical factors and is in turn associated with an increased risk of several human cancers."[102]

---

from foreign bodies, and that reactive oxygen species derived from inflammatory cells are one of the most important genotoxic mediators to accelerate the process.") (**Exhibit 72**); Liou and Storz, "Reactive oxygen species in cancer," *Free Radical Research* 44:479-496, at p. 479 (2010) ("Elevated rates of reactive oxygen species (ROS) have been detected in almost all cancers, where they promote many aspects of tumour developments and progression.") (**Exhibit 73**); Grivennikov et al., "Immunity, Inflammation, and Cancer," *Cell.* 140(6): 883-988, at p. 883 (2010) ("A role for inflammation in tumorigenesis is now generally accepted, and it has become evidence that an inflammatory microenvironment is an essential component of all tumors, including some which a direct causal relationship with inflammation is not yet proven.") (**Exhibit 74**); Crusz and Balkwill, "Inflammation and cancer: advances and new agents," *Nature* 12: 584-596, at p. 584 (2015) ("Chronic, dysregulated, persistent, and unresolved inflammation is associated with an increased risk of malignant disease.") (**Exhibit 75**); Reuter et al., "Oxidative stress, inflammation, and cancer: How are they linked?" *Free Radic Biol Med.* 49(11): 1603-1616 (2011) (recognizing that oxidative stress and chronic inflammation increase the risk of cancer) (**Exhibit 76**); Kiraly et al., "Inflammation-Induced Cell Proliferation Potentiates DNA Damage-Induced Mutations *In Vivo*," *PLOS Genetics* 11(2): 1-24 at p. 2 (2015) (**Exhibit 77**); Trabert et al., "Pre-diagnostic levels of inflammation markers and risk of ovarian cancer in the Prostate, Lung, Colorectal and Ovarian Cancer (PLCO) Screening Trial," *Gynecol Oncol.* 135(2): 297-304, at pp. 298, 309 (2014) ("Epidemiological evidence implicates chronic inflammation as a central mechanism in the pathogenesis of ovarian cancer….Our study provides additional evidence that inflammation plays an important roles in ovarian carcinogenesis.") (**Exhibit 78**); National Academic of Sciences, Engineering, and Medicine (2016), *Ovarian cancers: Evolving paradigms in research and care*, (IOM) Washington DC: The National Academic Press (**Exhibit 79**).

[101] Fernandes et al., "The Role of the Mediators of Inflammation in Cancer Development," *Pathol. Oncol. Res.* 21: 527-534, at p. 527 (2015) (**Exhibit 80**).

[102] Reuter et al. (2011) at p. 2, Ex. 76; Crusz and Balkwill (2015) at p. 584, Ex. 75 ("Almost 20% of human cancers are related to chronic inflammation caused by infections, exposure to irritants or autoimmune disease."); Coussens and Werb (2002) at p. 4, Ex. 71.

Chronic inflammation is associated with various stages of cancer development, including initiation, growth, and metastasis.[103] All cancers are caused by genetic mutations, including epithelial ovarian cancer.[104] Chronic inflammation leads to genetic mutations through cell proliferation, oxidative stress, and DNA damage.[105] Inflammatory environments contain cytokines and chemokines that contribute to cancer growth.[106] Inflammatory environments also generate reactive oxygen species ("ROS") and reactive nitrogen species ("RNS") that are actively mutagenic and cause DNA damage.[107]

---

[103] Balkwill and Mantovi (2001), at p. 539, Ex. 13; Reuter et al. (2011) at p. 5.

[104] Clarke-Pearson Amen. Rep. at 5, Ex. 8; Second Amended Rule 26 Expert Report of Shawn Levy, Ph.D. ("Levy Amen. Rep.") at 5 ("Cancer is a disease caused by DNA changes (mutations) that disrupt normal cell growth.") (**Exhibit 81**).

[105] *See* Coussens and Werb (2002), at p. 4 ("Functionally, many promoters, whether directly or indirectly, induce cell proliferation, recruit inflammatory cells, increase production of reactive oxygen species leading to oxidative DNA damage, and reduce DNA repair."); Okada (2007) at p. 2369, Ex. 72 ("Inflammatory environments due to the existence of foreign body cause a variety of biological responses as they contain increased growth/survival factors, chemotactic cytokines (chemokines), matrix metalloproteases, adhesion molecules, extracellular matrix, inflammatory mediators (i.e., histamine, eicosanoids, inflammatory cytokines and proteases, DNA-damage-promoting agents (i.e., ROS and RNS) and augmented angiogenesis."); Fernandes et al. (2015), at p. 537 ("[I]t is well established that chronic inflammation is strongly associated with several human cancers, since it leads to the release of pro-inflammatory cytokines, and other immunomodulatory, creating a favorable microenvironment for tumor progression and metastasis.").

[106] Coussens and Werb (2002), at p. 4, Ex. 71; Okada (2007) at p. 2369, Ex. 72.

[107] Yan et al., "Molecular analysis of genetic instability," *Cancer* 512: 15-28, at p. 16 (2006) (inflammation induces ROS which causes "genetic aberrations and leads to transformation") (**Exhibit 82**); Hanahan, D. and Robert A. Weinberg, "Hallmarks of Cancer: The Next Generation," *Cell* 144: 646-674, at p. 659 (2011) ("[I]nflammatory cells can release chemicals, notable reactive oxygen species, that are actively mutagenic for nearby cancer cells, accelerating their genetic evolution toward states of heightened malignancy.") (**Exhibit 83**); Okada (2007) at p. 2369; Clarke-Pearson Amen. Rep. at 5, Ex. 8; Wolf Amen. Rep. at 15, Ex. 7; Smith Rep. at 17, Ex. 17; Levy Amen. Rep. at 13, Ex. 81; Singh Rep. at 58, Ex. 52; Siemiatycki Rep. at 65, Ex. 18.

This inflammatory cascade is shown to occur in the pathogenesis of epithelial ovarian cancer.[108] The tumor environment in which epithelial ovarian cancer develops has a broad spectrum of pro-inflammatory cytokines and chemokines.[109] "At sites of inflammation, epithelial cells are exposed to increased levels of inflammatory mediators such as reactive oxygen species [ROS], cytokines, prostaglandins, and growth factors that contribute to increased cell division, and genetic and epigenetic changes."[110]

Furthermore, studies in which generations of ROS was inhibited showed cell death to proceed normally,[111] further supporting the role of ROS (and thus,

[108] Savant et al., at Figure 1, Ex. 12 (2018) ("Unresolved, chronic inflammation is a critical risk factor in [ovarian] tumor initiation."); Ness, Roberta B. and Carrie Cottreau, "Possible Role of Ovarian Epithelial Inflammation in Ovarian Cancer," *J. of the Nat'l Cancer Inst.* 91: 1459-1467, at p. 1463 (1999) (**Exhibit 84**); Sept. 30, 2004 Fax from Luzenac Director of Product Safety to Bill Ashton from JNJ (discussing Ness as offering "some compelling evidence in support of the 'migration' hypothesis") (**Exhibit 85**); Saed et al., "Updates on the role of oxidative stress in the pathogenesis of ovarian cancer," *Gynecologic Oncology* 145: 595-602, at p. 596-97 (2017) (**Exhibit 86**); Shan, et al., at p. 3110 ("Increasing evidence suggests that inflammation contributes significantly to the etiology of EOC.") Ex. 14; Saed, Morris and Fletcher (2018), "New Insights into the Pathogenesis of Ovarian Cancer: Oxidative Stress," *Ovarian Cancer – From Pathogenesis to Treatment* Chapter 4 (**Exhibit 87**).

[109] Freedman et al., "Peritoneal inflammation – A microenvironment for Epithelial Ovarian Cancer (EOC)," *J. of Translational Med.* 2: 1-10, at p. 4 (2004) (**Exhibit 88**); Shan and Liu (2009), at p. 3130, Ex. 14 ("The tumor milieu in which EOC develops has been described as one enriched with a broad spectrum of pro-inflammatory cytokines and chemokines.").

[110] Savant et al. (2018), at p.1, Ex. 12.

[111] Jiang, Z., Nicole M. Fletcher, Rhouba Ali-Fehmi, Michael P. Diamond, Husam M. Abu-Soud, Adnan R. Munkarah, and Ghassan M. Saed, "Modulation of redox signaling promotes apoptosis in epithelial ovarian cancer cells," *Gynecol Oncol.* 122(2): 1-17, at p. 8 (2011) (**Exhibit 89**); *see also* Belotte et al. 2014, "The Role of Oxidative Stress in the Development of Cisplatin Resistance in Epithelial Ovarian Cancer," *Reproductive Sciences* 21(4): 503-508, at p. 505-506 (2014) (**Exhibit 90**).

inflammation) in increased cell growth and cancer progression. Myeloperoxidase also is released by epithelial ovarian cancer cells in response to inflammation and is indicated to play a role in the progression of carcinogenesis by promoting cell death.[112] Inhibiting myeloperoxidase likewise leads to normal cell death.[113]

Second, asbestos is a known carcinogen that causes ovarian cancer.[114,] IARC also recently classified talc as "probably carcinogenic to humans" based on the "'strong' mechanistic evidence in human primary cells and experimental systems."[115] J&J's own experts agree that talc and asbestos cause chronic inflammation and that asbestos is carcinogenic.[116]

Additionally, *in vitro* and *in vivo* studies have shown that talc and asbestos cause inflammation and oxidative stress in human and animal cells.[117] *In vitro*

---

[112] Fletcher, N., Zhonglian Jiang, Rhouba Ali-Fehmi, Nancy K. Levin, Jimmy Belotte, Michael A. Tainsky, Michael P. Diamond, Hasam M. Abu-Soud, and Ghassan M. Saed, "Myeloperoxidase and free iron levels: Potential biomarkers for early detection and prognosis of ovarian cancer," *Cancer Biomarkers* 10:267-275, at p. 268 (2011) (**Exhibit 91**); Saed et al., "Myeloperoxidase serves as a redox switch that regulates apoptosis in epithelial ovarian cancer," *Gynecol Onco.* 116(2): 1-14, at p. 6 (2010) (**Exhibit 92**).

[113] Fletcher, Saed et al. (2011), at p. 268.

[114] IARC 2012 at pp. 219, 232, 256, 280, Ex. 25; *see also* Reid et al., "Gynecologic and Breast Cancers in Women After Exposure to Blue Asbestos in Wittenoom," *Cancer Epidemiology, Biomarkers & Prevention* 18: 140-147 (2009) (**Exhibit 93**).

[115] *IARC Monographs* 2024, at p. 1, Ex. 2.

[116] Holcomb Dep. at 174:11-18, Ex. 31 (concedes that talc causes chronic inflammation); *see also* Huncharek et al., at p. 427, Ex. 28 (2007) ("If one is exposed to a mixture of talc and asbestos, it is reasonable to expect a carcinogenic effect as it contains a known carcinogen.").

[117] Radic et al., "Immunosuppression induced by talc granulomatosis in the rat," *Clin. Exp. Immunol.* 73: 316-321 (1988) (talc granulomas initiated whole-animal immune suppression in rats) (**Exhibit 94**); National Toxicology Program, "Toxicology and Carcinogenesis Studies of Talc," U.S. Dept. of Health and Human Servs., No. 421 at pp. 11, 56 (1993) (in inhalation study of talc

studies also document inflammatory and pro-carcinogenic biologic effects in cell cultures exposed to talcum powder. These studies include Shukla[118] (demonstrating genotoxicity in both asbestos and nonfibrous talc), Buz'Zard[119] (demonstrating aberrant ROS [reactive oxygen species] and neoplastic transformation), Akhtar[120]

"[t]here was clear evidence of carcinogenic activity of talc in female" rats and finding "principal toxic lesions associated with inhalation exposure to the same concentrations of talc in rats included chronic granulomatous inflammation") (**Exhibit 95**); Keskin et al. (2009) "Does long-term talc exposure have a carcinogenic effect on the female genital system of rats? An experimental pilot study." at p. 926 (foreign body reaction, infection and increased inflammatory cells were found in all rats exposed to talc) (**Exhibit 96**); Kahn et al., "Nano-talc Stabilized TNF- m-RNA I Human Macrophages," *J of Biomedical Nanotechnology* 7: 112-113, at p.113 (2011) ("Observations clearly demonstrated the inflammatory potential of [nano talc] particles which might be at least partial and potential mechanism in talc mediated pathogenicity in the exposed population.") (**Exhibit 97**); Ghio et al., "Disruption of Iron Homeostasis in Mesothelial Cells after Talc Pleurodesis," *Am J Respi Cell Mol Biol* 46: 80-86, at p. 80 (2012) ("[E]xposure to talc was associated with a time-dependent and concentration-dependent generation of oxidants in both cells types. The expression of proinflammatory mediators was also increased after *in vitro* exposures of mesothelial and airway epithelial cells to talc.") (**Exhibit 98**); Akhtar et al., "Cytotoxicity and Apoptosis Induction by Nanoscale Talc Particles from Two Different Geographical Regions in Human Lung Epithelial Cells," *Environmental Tox* 394-406, at p. 404 (2014) (talc particles "significantly induced cytotoxicity, oxidative stress, and apoptosis in human lung epithelial cells") (**Exhibit 99**); Levy Amen. Rep. at 16, Ex. 81; Smith Rep. at 17, Ex. 17; Clarke-Pearson Amen. Rep. at 6, Ex. 8; Wolf Amen. Rep. at 16, Ex. 7; Plunkett Amen. Rep. at 45-46, Ex. 50; Moorman Rep. at 34, Ex. 16; Singh Rep. at 59, Ex. 52; Siemiatycki Amen. Rep. at 74, Ex. 18; McTiernan Amen. Rep. at 91, Ex. 15; Carson Rep. at 5, Ex. 51.

[118] Shukla, Arti, Maximilian B. MacPherson, Jedd Hillegass, Maria E. Ramos-Nino, Vlada Alexeeva, Pamela M. Vacek, Jeffrey P. Bond, Harvey I. Pass, Chad Steele, and Brooke T. Mossman, "Alterations in Gene Expression in Human Mesothelial Cells Correlate with Mineral Pathogenicity," *American Journal of Respiratory Cell and Molecular Biology* 41:114-123 (2009) (**Exhibit 100**).

[119] Buz'Zard and Lau, "Pycnogenol reduces Talc-induced Neoplastic Transformation in Human Ovarian Cell Cultures," *Phytother. Res.* 21: 579-586, at p. 585 (2007) (**Exhibit 101**) ("The data show that talc is capable of increasing cell proliferation, inducing neoplastic transformation of both the normal stromal and epithelial ovarian cells *in vitro*; and increasing ROS generation in these cells as well as the PMN cells.").

[120] Akhtar et al. (2014) at p. 404, Ex. 99 (talc particles "significantly induced cytotoxicity, oxidative stress, and apoptosis in human lung epithelial cells").

(demonstrating induced cytotoxicity, oxidative stress, and apoptosis), and Akhtar[121] (demonstrating toxicity mediated through oxidative stress). Fletcher (2019) exposed 5-6 cell lines including normal fallopian tube and ovarian cells, as well as ovarian cancer cells, to J&J baby powder, finding alteration in the redox state indicating oxidative stress, elevation in CA-125 levels, enhanced cell proliferation, inhibited apoptosis, changes in gene expression, and inducement of SNPs (single nucleotide polymorphisms) in a dose-responsive fashion.[122]

Recently, Harper and colleagues also demonstrated that exposure to J&J's baby powder also causes p53 mutations, cell proliferation, and malignant transformation in normal epithelial cells.[123] Mandarino et al. (2020) found that talc, especially in combination with estradiol, stimulated microphages to produce increased reactive oxygen species and changes in gene expression that could promote a pro-tumorigenetic environment.[124] And Emi et al. (2021) conducted a

[121] Akhtar, Mohd Javed, Sudhir Kumar, Ramesh Chandra Murthy, Mohd Ashquin, Mohd Imran Khan, Govil Patil, and Iqbal Ahmad. "The Primary Role of Iron-Mediated Lipid Peroxidation in the Differential Cytotoxicity Caused by Two Varieties of Talc Nanoparticles on A549 Cells and Lipid Peroxidation Inhibitory Effect Exerted by Ascorbic Acid." *Toxicology in Vitro: An International Journal Published in Association with BIBRA* 24, no. 4 (June 2010): 1139–47. (**Exhibit 102**).

[122] Fletcher, NM, Amy K. Harper, MD, Ira Memaj, BS, Rong Fan, MS, Robert T. Morris, MD, and Ghassan M. Saed, PhD. "Molecular Basis Supporting the Association of Talcum Powder Use With Increased Risk of Ovarian Cancer." Reproductive Sciences 1-10. (2019). (**Exhibit 103**).

[123] Harper et al., "Talcum Powder Induces Malignant Transformation in Normal Human Primary Ovarian Epithelial Cells," Minerva Obstet. Gynecol. 75:150-157 (2023). (**Exhibit 104**).

[124] Mandarino et al., "The effect of talc particles on phagocytes in co-culture with ovarian cancer cells," *Environ Res.* 180 (2020). (**Exhibit 105**)

follow up study that found talc induced substantially more gene expression changes in comparison to the control and thus, the "pathway affected by talc included cell proliferation, immune responses and signaling, immunosurveillance, apoptosis."[125] These studies provide important evidence of the effects of talcum powder at the molecular level.

J&J again ignores the weight of the evidence and instead, selectively chooses a handful of studies that J&J says do not show inflammation. Pointing to Heller et al (1996–talc) and Henderson et al. (1971), J&J argues that inflammation is not caused by talc because inflammation has never been visually observed in pathology.[126] This has nothing to do with *Daubert*. Whether Plaintiffs are correct, or J&J is correct is a matter for the jury, not an issue to be decided on *Daubert*.[127]

Nonetheless, it is well accepted that inflammation is not necessarily seen by histology in the biologic cascade resulting in carcinogenesis.[128] Oxidative stress and

---

[125] Emi et al., "Transcriptomic and epigenomic effects of insoluble particles on J774 macrophages," *Epigenetics* 16:1053-1070 (2021). (**Exhibit 106**)

[126] Mem. at 28-29.

[127] *Milward*, 639 F.3d at 15; *Daubert v. Merrell Dow Pharm., Inc.*, 43 F.3d 1311, 1318 (9th Cir. 1995) (*Daubert* II) ("[T]he *Daubert* test "is not the correctness of the expert's conclusion but the soundness of his methodology.").

[128] Hallmarks of Cancer at p. 58, Ex. 83 (authors note that inflammation is not necessarily seen by histology. Oxidative stress is not seen); Clarke-Pearson 2019 Dep. at 228:8-17, Ex. 65 (explaining that inflammatory cascade is not necessarily visual in histology); Levy 2019 Dep. at 258:2-259:14, Ex. 20 (explaining that whether you visually see the inflammatory response will vary from person to person and depends on timing, magnitude of inflammatory response, and methodology for detection, including a ROS assay).

genetic mutations are not typically associated with histologic findings. Additionally, by the time tissue is observed, any inflammation that may have been visual would likely have been consumed by the cancer over time.[129] Still, inflammatory biomarkers like CA-125 may be observed and ovarian cancer is almost always associated with ascites which is an inflammatory consequence of ovarian cancer.[130]

J&J also critiques a handful of animal studies relied on by the PSC's experts as only showing acute inflammation, not chronic inflammation. To be clear, the PSC's experts rely on *in vitro* and *in vivo* studies, not simply animal studies.[131] Additionally, Keskin (2009) involved rats and application of talc (asbestos-free) only for only three months.[132] Given the study limits in Keskin (2009), it is not surprising that only infection and acute granulomas were shown.[133] The PSC's

[129] Kane Rep. at 12, Ex. 57 ("Remote exposure will not necessarily mean there will be evidence of current inflammation or foreign body reaction when tissues are examined.").

[130] Clarke-Pearson 2019 Dep. at 226:18-227:5, Ex. 65.

[131] *See* Clarke-Pearson Amen. Rep. at 5-6, Ex. 8; Smith Rep. at 17, Ex. 17; Wolf Amend. Rep. at 15-17, Ex. 7; Carson Rep. at 6, Ex. 51; Singh Rep. at 58, Ex. 52; McTiernan Rep. at 60-61, Ex. 15; Plunkett Rep. at 42, Ex. 50; Moorman Rep. at 33-34, Ex. 16.

[132] Keskin et al. (2009) at p. 925, Ex. 96; *see* Health Canada, Screening Assessment Talc, p. 23, Ex. 1 ("There were no cancer or pre-cancer effects observed; however, the authors noted that the study duration may have been too short to note these types of effects.").

[133] Health Canada, Screening Assessment Talc, p. 23 ("While some animal studies have investigated the effect of talc on the ovaries, rodents are poor experimental models for perineal studies for a number of reasons. Ovulation, including the number of oocytes general and the length of cycle, is markedly different in rodents compare to humans (Chaffin and VandeVoort 2013). In general, epithelial tumours are rare in rodents…On account of the limitations detailed above, in addition to the challenges posed by exposing animals via the perineal route, animal data are very limited.").

experts' opinions have to do with human females with long-term use of talcum powder (which also contains platy talc, asbestos, fibrous talc, heavy metals, and other chemicals). Despite the limited time frame in Keskin, the study authors still noted "foreign body reaction" and "increase in inflammatory cells" in all of the exposed rats.[134] While chronic inflammation was not seen in the limited study time, the study results are consistent with the conclusion that talcum powder can cause chronic inflammation.

J&J also criticizes reliance on rat experiments by the National Toxicology Program (NTP).[135] J&J argues that these studies only found cancer in the lungs and adrenal glands and not ovaries. However, as explained by Dr. Plunkett, because the rodents were exposed through inhalation, "the studies would not be expected to produce ovarian tumors in rats or mice…."[136] Additionally, while it is recognized that rodents provide "poor experimental models for perineal studies,"[137] the NTP results are indicative of talc's role in carcinogenesis.[138]

Finally, J&J faults the PSC's experts for pointing to pleurodesis (injection of talc into the lungs) as evidence that talc causes chronic inflammation. According to

[134] Keskin et al. (2009) at p. 925.

[135] Mem. at 29-20.

[136] Plunkett Amen. Rep. at 45, Ex. 50.

[137] Health Canada, Screening Assessment Talc, at p. 23, Ex. 1.

[138] Plunkett Amen. Rep. at p. 45.

J&J, pleurodesis only creates acute inflammation and there is no evidence it causes cancer in treated patients.[139] J&J is wrong on both points. Pleurodesis is used to treat chronic pleural effusion most commonly the result of metastatic cancer, including lung, ovary, and breast cancers. The median survival following diagnosis ranges from 3 to 12 months.[140] Thus, any ability to study the long-term effects of pleurodesis is significantly compromised.

Additionally, pleurodesis causes both acute *and* chronic inflammation. Talc is used in pleurodesis for its sclerosant properties, resulting in obliteration of the pleural space.[141] This process is systemic, as well as localized in the pleura.[142]

---

[139] Mem. at 30-31.

[140] Roberts et al., "Management of a malignant pleural effusion: British Thoracic Society pleural disease guideline 2010," *Thorax* 65:32-40 (2010) (**Exhibit 107**).

[141] Sclerosis is a pathological condition in which a tissue has become hard, and which is produced by overgrowth of fibrous tissue and other changes (as in arteriosclerosis) or by increase in interstitial tissue (as in multipole sclerosis). https://www.merriam-webster.com/dictionary/sclerosis#medicalDictionary (accessed on August 19, 2024).

[142] Ghio et al., 46:80-86, Ex. 98 (2012) ("This research concerns the disruption in iron homeostasis that occurs in the pleura and lungs of patients treated with talc pleurodesis. The accumulation of this metal, the accompanying oxidative stress, and inflammatory events after exposure to talc are comparable to those with other forms of particulate matter. Pleurodesis can function as a model of particle-related biological effect."); Genofre et al., "Talc pleurodesis: Evidence of systemic Inflammatory response to small size talc particles," *Respiratory Medicine*, 103:91-97 (2009) (**Exhibit 108**) ("In a second step, the presence of talc particles in tissues would trigger a local cellular response that contributes to the maintenance and amplification of the systemic inflammatory response."); Vannucci et al., "Observational analysis on inflammatory reaction to talc pleurodesis: Small and large animal model series review," *Experimental and Therapeutic Medicine*, 15:733-738 (2018) (**Exhibit 109**) ("Talc is the most used sclerosing agent worldwide for achieving pleural space obliteration. Though its efficacy has been widely reported especially in neoplastic effusion, severe inflammatory reactions have been described both acute and long-term.").

Researchers have also advised against the usage of talc for pleurodesis because of the risk of asbestos contamination.[143] As such, pleurodesis is highly relevant to the discussion of inflammation as part of a biologically plausible mechanism by which talcum powder can cause the development of ovarian cancer.

The totality of the scientific evidence reliably supports the PSC's experts' opinions that talcum powder can cause chronic inflammation that leads to an increased risk of ovarian cancer.

2. The In Vitro Evidence Supports the Opinion that Talcum Powder Causes Chronic Inflammation and Oxidative Stress

J&J argues that the PSC's experts cannot rely on in vitro cell studies because they are not performed on live humans.[144] Not so. As Judge Wolfson recognized, "[c]ourts have generally determined that '*in vitro* tests provide useful information about metabolic processes at a cellular level, and may supplement existing animal

[143] Ghio, Correspondence "Talc Should Not Be Used for Pleurodesis in Patients with Nonmalignant Pleural Effusions," (2001) (**Exhibit 110**) ("[T]here should continue to be concern regarding the use of talc for pleurodesis in individuals with nonmalignant pleural effusions and spontaneous pneumothorax. This dilemma results from a possible increased risk of malignant mesothelioma in those patients treated with talc."); Ferrer et al., "Influence of Particle Size on Extrapleural Talc Dissemination After Talc Slurry Pleurodesis," *Chest*, 122:1018-1027 (2002) ("Thus, it seems preferable not to treat patients with benign pleural diseases with intrapleural talc, since the long-term effects of this mineral have not been definitively established… [I]t seems advisable to eliminate particles less than10 micrometers [present in talcum powder] to avoid phagocytosis-related inflammation [chronic]."). (**Exhibit 111**).

[144] Mem. at 31.

and human data.'"[145] In vitro studies are particularly important in cases like this where in vivo studies cannot be performed due to ethical issues.[146]

J&J also attacks the PSC's reliance on Fletcher 2019, contending that it cannot reliably support their opinions because it came from Dr. Saed's laboratory.[147] Fletcher (2019) is consistent with other cell studies finding that exposing human cells to talc increases ROS.[148] Judge Wolfson did not find that studies from Dr. Saed's laboratory are unreliable. To the contrary, Judge Wolfson found that J&J's attacks on Dr. Saed's credibility "do not fundamentally undermine the methodologies" he used.[149] J&J offers nothing new on this point.

Judge Wolfson also properly rejected J&J's argument regarding dose, finding Dr. Saed used doses "'similar' to doses used in published studies that discuss 'testing talcum powder and determining whether the powder has a biological effect in cells.'"[150] J&J still does not identify a different dose that should be used. Indeed, its own expert testified that the doses used by Dr. Saed "are 'appropriate concentration levels to determine pathogenicity of asbestos and talc.'"[151] Because Fletcher (2019)

---

[145] *In re Johnson & Johnson*, 509 F. Supp. 3d at 143.

[146] *See id.* at 175.

[147] Mem. at 32.

[148] *See* McTiernan Amen. Rep. at 91, Ex. 15 (discussing Fletcher (2019) and other cell studies).

[149] *In re Johnson & Johnson*, 509 F. Supp. 3d at 146.

[150] *Id.* (citing Shukla (2009), Buz'Zard (2007), Akhtar (2010), and Akhtar (2012)).

[151] *Id.*

is relied on solely to show that talc may cause inflammation in cells, any "failure to use a relevant dosage that mimics actual human use in an *in vitro* study does not render the study regarding inflammation unreliable."[152]

3. The Scientific Evidence Supports the Opinion that Chronic Inflammation Increases the Risk of Ovarian Cancer

J&J again ignores the evidence, arguing that the PSC's experts "lack reliable evidence to show that chronic inflammation can cause any kind of ovarian cancer."[153] J&J claims that the "review articles" on which the PSC's experts rely do not support their opinions. Not so.

Ness and Cottreau (1999) did not pull the idea that inflammation plays an important role in the pathogenesis of ovarian cancer out of thin air. Inflammation as a mechanism of cancer has been well known for decades.[154] Ness and Cottreau did a thorough analysis of the available data on inflammation and cancer and the mechanisms known to relate to ovarian cancer, and concluded in 1999 that various

[152] *Id.* at 143; *see*, *e.g.*, Clarke-Pearson Amen. Rep. at 6, Ex. 8 ("These studies provide evidence of chronic inflammation in animals and cells when exposed to talcum powder and support the findings of experiments with Johnson's Baby Powder."); McTiernan Amen. Rep. at 91-93, Ex. 15 (discussing Fletcher (2019) among totality of the evidence and finding "based on these studies, that talc and asbestos induced inflammation which results in cell proliferation, inhibition of apoptosis, and secretion of mediators, that may promote tumorigenesis. This adds to the weight of evidence…").

[153] Mem. at 36.

[154] *See* Balkwill and Mantovani (2001) at p. 539, Ex. 13 (recognizing that as far back as 1863, inflammatory cells (leukocytes) were identified in tumor tissue).

inflammatory factors, including exposure to asbestos and talcum powder, are epithelial inflammation initiators that play a role in ovarian carcinogenesis.[155]

Subsequent scientists have done additional research and concluded that inflammation plays a critical role in the pathogenesis of epithelial ovarian cancer. For example, in 2009 Shan and Liu found that "[t]he tumor milieu in which EOC develops has been described as one enriched with a broad spectrum of pro-inflammatory cytokines and chemokines…Increasing evidence suggests that inflammation contributes significantly to the etiology of EOC"; in 2014 Trabert et al. found "evidence that inflammation plays an important role in ovarian carcinogenesis"; and in 2018, Health Canada found that "[t]here is support for an association of inflammation and increased risk of ovarian cancer"; and Savant et al. (2018) "presented published evidence suggesting that inflammation and inflammatory mediators promote ovarian tumorigenesis."[156]

J&J ignores the vast majority of relevant and reliable evidence supporting inflammation as a mechanism of ovarian cancer. Instead, discussing only two studies – Trabert and Buz'Zard – J&J argues the studies undercut the PSC's expert's opinions. In Trabert, even though the results were inconclusive the authors

[155] Ness and Cottreau (1999) at p. 1464, Ex. 84 (discussing review of the data on inflammation).

[156] *See* Shan and Liu (2009) at p. 3130, Ex. 14; Trabert et al. (2014-inflammation markers) at pp. 309, Ex. 78; Health Canada. Screening Assessment Talc, at p. 20, Ex. 1; Savant et al. (2018) at p. 18, Ex. 12; *see also* Freedman et al. (2004) at p. 4, Ex. 88; Saed et al. (2017) at pp. 596-97. Ex. 86.

recognized that "[m]ultiple lines of evidence suggest that ovarian cancer may be related to chronic inflammation…[I]nflammation-related exposures such as endometriosis and exposure to talc or genital powder and asbestos have been associated with increased ovarian risk."[157]

J&J argues Buz'Zard showed a decrease in ROS levels for immortalized cells treated with talc. However, Buz'Zard found that "ROS generation increased with time in the talc treated [normal] cells."[158] J&J provides no explanation for why the use of immortalized cells eliminates these results. Based on this data, the authors concluded that "[t]he data show that talc is capable of increasing cell proliferation, inducing neoplastic transformation of both the normal stromal and epithelial ovarian cells *in vitro*; and increasing ROS generation in these cells as well as the PMN cells."[159] Additionally, as to cellular transformation, the authors explained: "Our data show talc not only increased cell viability (Fig. 1A), but also caused an increased in transformed cells in both the stromal *and* epithelial ovarian cells by their ability to grow, divide and form colonies while being suspended in soft agar."[160] These results are relevant.

---

[157] Trabert et al., "Aspirin, Nonaspirin Nonsteroidal Anti-inflammatory Drug, and Acetaminophen Use and Risk of Invasive Epithelial Ovarian Cancer: A Pooled Analysis in the Ovarian Cancer Association Consortium," *JNCI J Natl Cancer lnst.* 106(2): 1-11, at p. 1 (2014) (**Exhibit 112**).

[158] Buz'Zard and Lau (2007) at p. 582, Ex. 101.

[159] *Id.* at p. 585.

[160] *Id.* at p. 584.

J&J also criticizes some experts for citing studies regarding the role anti-inflammatories ("NSAIDs") play in decreasing cancer risk.[161] J&J argues that because the results of the NSAID studies are mixed, the PSC's experts cannot rely on them. The PSC's experts do not rely on NSAID data for their opinions on inflammation – they rely on the overwhelming body of evidence that demonstrates inflammation plays an important role in the pathogenesis of ovarian cancer. The PSC's experts that cite to the NSAID data acknowledge its mixed results and only cite it as additional evidence of the role of inflammation in cancer pathogenesis generally.[162] The evidence supports this opinion.

J&J points to work by Trabert as not being supportive of the PSC's experts' opinions.[163] To the contrary, Trabert's NSAID study observed a 20% risk reduction for daily users of aspirin and 34% risk reduction for regular users of low-doses of

[161] Mem. at 40.

[162] *See* Wolf Amen. Rep. at 16, Ex. 7 ("Although the literature is still somewhat contradictory, aspirin and other non-steroidal anti-inflammatory drugs have been shown to prevent and treat certain types of cancer, particularly colorectal."); Smith Rep. at 18, Ex. 17 ("Although somewhat inconsistent, data regarding NSAID and aspirin suggest a protective effect…No study found an effect on ovarian cancer…."); Levy Amen. Rep. at 14, Ex. 81 ("The earlier studies focusing on NSAIDs were preliminary and results were somewhat inconsistent."); McTiernen Amen. Rep. at 90, Ex. 15 (citing NSAID data for "f[]urther evidence of the inflammation mechanism"); Kane Rep. at 12, Ex. 57 ("There also are some studies showing a protective effect of anti-inflammatory drugs on the risk of developing carcinoma, although some studies have failed to show a protective effect.").

[163] Mem. at 40.

aspirin.[164] The authors identified inflammation reduction as a plausible mechanism.[165]

In the same year (2014), Trabert et al. also performed a case-control study measuring 46 inflammation-related biomarkers in ovarian cancer cases and matched controls.[166] In this study, the researchers identified several circulating inflammation markers that were associated with risk of developing cancer between 2 and 14 years later.[167] The authors again identify inflammation as plausible mechanism.[168]

Trabert and the Ovarian Cancer Cohort Consortium published a pooled analysis of 12 case-control studies in 2019, confirming the slightly lower but statistically significant, decrease in ovarian cancer risk with regular aspirin use –

[164] Trabert et al. (2014-NSAIDs) at p. 5, Ex. 112.

[165] *Id.* ("Several established risk factors for ovarian cancer are related to inflammatory processes. During ovulation, follicles rupture and inflammatory mediators are released locally that may initiate cell transformation or that may promote growth of transformed cells. Proinflammatory agents are also released in inflammatory processes related to endometriosis. Aspirin and nonaspirin NSAIDs may reduce exposure to these inflammatory processes; thus, the reduced risk of ovarian cancer with frequent aspirin use and nonaspirin NSAID use is consistent with the hypothesized inflammatory etiology of ovarian cancer.") (citations omitted).

[166] Trabert et al. (2014-inflammation markers), Ex. 78.

[167] *Id.* at p. 6.

[168] *Id.* at p. 2 ("Epidemiologic evidence implicates chronic inflammation as a central mechanism in the pathogenesis of ovarian cancer, the most lethal gynecologic cancer among women in the United States. Chronic inflammation can induce rapid cell division, increasing the possibility for replication error, ineffective DNA repair and subsequent mutation. Ovarian cancer has been linked to several events and conditions which are related to inflammation and repair, including incessant ovulation, endometriosis, exposure to talc and asbestos, and in some studies pelvic inflammatory disease. In addition, reduced risks found for aspirin use could be related to direct anti-inflammatory actions, while reduced risks related to tubal ligation and hysterectomy could reflect limited exposure to environmental causes of inflammation.") (citations omitted).

similar to the risk reduction observed in case-control analyses.[169] The authors again identify inflammation as a plausible mechanism.[170]

Additionally, a study of analgesic medication use and the risk of epithelial ovarian cancer in African American women, published in 2016, recognized the inconsistency in the literature, "with the majority of studies showing an inverse association."[171] In this study, aspirin use, overall, was associated with a 44% lower EOC risk.[172] The authors concluded that this study "supports previous evidence that any NSAID use, but not acetaminophen [not an anti-inflammatory agent] is inversely associated with EOC risk.[173] These authors also identify inflammation as the plausible mechanism.[174] Although research is ongoing regarding the role of anti-inflammatory agents in reduction of ovarian cancer risk, these studies support the importance of inflammation in the etiology of epithelial ovarian cancer.

---

[169] Trabert et al., "Analgesic Use and Ovarian Cancer Risk: An Analysis in the Ovarian Cancer Cohort Consortium," *J Nat Cancer Inst.* 111(2): 1-9, at p. 8 (2019) (**Exhibit 113**).

[170] *Id.* at p. 2. ("Chronic inflammation likely plays a key role in ovarian carcinogenesis. Factors associated with epithelial disruption through ovulation, inflammation-related exposures such as endometriosis and pelvic inflammatory disease, and circulating biomarkers of inflammation have been associated with ovarian cancer risk.")

[171] Peres et al., "Analgesic medication use and risk of epithelial ovarian cancer in African American women," *British J. of Cancer* 114: 819-825 (2016) (**Exhibit 114**).

[172] *Id.* at p. 819.

[173] *Id.* at p. 824.

[174] *Id.* at 820 "Inflammation may play a role in ovarian cancer carcinogenesis through the production of toxic oxidants and bioactive substances, increasing the chances of DNA damage and mutagenesis. Analgesic drugs, such as aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs), have anti-inflammatory properties and have been associated with reduced risks of several malignancies.) (citations omitted).

In a recent meta-analysis of cohort and case-control studies by Hurwitz et al. (over thirty authors from the Ovarian Cancer Cohort Consortium, including Trabert), frequent aspirin use was found to reduce ovarian cancer by 13%.[175]

J&J's critique of Phung et al. (2022) also has no merit.[176] J&J claims that Phung did not show any significant interaction between talc and endometriosis. However, Phung concluded that "[g]enital talc use was also positively associated with risk for women with and without endometriosis, although its magnitude seemed to be greater for women with than women without."[177] The authors further explained that the role inflammation play in the development of cancer is "in line with our observation of a higher risk associated with genital talc use for women with endometriosis since inflammation has been proposed as a possible biological mechanism for talc's association with ovarian cancer."[178]

Finally, J&J criticizes the PSC's experts for relying on Harper et al. (2023) because some journal reviewers provided criticisms for the paper before it was published. The peer review process is intended to ensure an article is ready for

---

[175] Hurwitz et al. (2022) J Clin Oncol Published by American Society of Clinical Oncology ("Chronic inflammation likely plays a key role in ovarian carcinogenesis… In conclusion, this study, the largest to date on frequent aspirin use and ovarian cancer, supports a 13% reduction in ovarian cancer risk with frequent aspirin use, with a 14% reduction for high-grade serous carcinoma, the most common and one of the more lethal histotypes.") (**Exhibit 115**).

[176] Mem. at 39.

[177] Phung et al., "Effects of risk factors for ovarian cancer in women with and without endometriosis," *Fertil Steril* 118:960-969 (2022). (**Exhibit 116**)

[178] *Id.*

publication, providing researchers with feedback that can be evaluated and incorporated into a manuscript as appropriate. However, each reviewer comes with their own biases and expertise. Nothing is known about the reviewers J&J cites that provided criticisms for Harper (2023) before it was published. It is also unknown whether aspects of the reviewer comments were incorporated into the final, published article. Harper (2023) is just one of many studies with similar findings relied on by the PSC's experts.[179]

D. MACROPHAGE STUDIES SUPPORT THE OPINION THAT TALCUM POWDER CAUSES OVARIAN CANCER

J&J again isolates two studies (Mandarino et al. (2020) and Emi et al. (2021)) to argue that the theory that talc negatively impacts macrophages is too speculative.[180] The PSC's experts do not rely on Mandarino or Emi in isolation as a basis for a new theory of biological plausibility. Rather, Mandarino and Emi are considered in the context of the totality of the evidence as evidence of talc's ability to initiate cellular changes that can lead to cancer.

Macrophages are the first immune cells to clear foreign bodies from a cell and destroy malignant cells.[181] Mandarino and Emi both tested the effect talc, in

[179] *See*, *e.g.*, McTiernan Amen. Rep. at 91, Ex. 15; Clarke-Pearson Amen. Rep. at 5-6, Ex. 8; Smith-Bindman Amen. Rep. at 10, Ex. 19.

[180] Mem. at 45-46.

[181] Emi et al. (2021) at p. 1053, Ex. 106; Mandarino et al. (2020) at p 2, Ex. 105; Smith-Bindman Amen. Rep. at 14, Ex. 19.

combination with estrogen, had on reducing the anti-tumor abilities of macrophages. Emi et al. found that in vitro "exposure to talc particles alone, and especially to a combination of talc with oestrogen leads to substantial genome-wide gene expression changes."[182] This is significant because the cellular pathways impacted were those involved in cellular proliferation, immune response and regulation, and enzymes and proteins of epigenetic regulation.[183]

Similarly, Mandarino et al. (2020) found "talc alone and especially in combination with [estrogen] produced changes in gene expression that may promote pro-tumorigenic environment and less efficient surveillance (tumoricidal) activity of the macrophages."[184] The noted changes in expression of macrophage genes are pertinent to cancer development.[185]

These studies, together with the other substantial evidence on inflammation, reliably support the PSC's experts' opinions on biological plausibility.

IV. CONCLUSION

For the foregoing reasons, J&J's motion to exclude the PSC's experts' opinions related to biological plausibility once again should be denied in its entirety. J&J's veiled request for reconsideration has no legs to stand on.

[182] Emi et al. (2021) at p. 1064.

[183] Smith-Bindman Amen. Rep. at 14.

[184] Mandarino et al. (2020) at p. 6.

[185] Smith-Bindman Amen. Rep. at 14.

Respectfully submitted,

/s/ *Michelle A. Parfitt*
Michelle A. Parfitt
ASHCRAFT & GEREL, LLP
1825 K Street, NW, Suite 700
Washington, DC 20006
Tel: 202-783-6400
Fax: 202-416-6392
mparfitt@ashcraftlaw.com

/s/ *P. Leigh O'Dell*
P. Leigh O'Dell
BEASLEY, ALLEN, CROW, METHVIN, PORTIS & MILES, P.C.
218 Commerce Street
Montgomery, AL 36104
Tel: 334-269-2343
Fax: 334-954-7555
Leigh.odell@beasleyallen.com
Plaintiffs' Co-Lead Counsel

/s/ *Christopher M. Placitella*
Christopher M. Placitella
COHEN, PLACITELLA & ROTH, P.C.
127 Maple Avenue
Red Bank, NJ 07701
Tel: 732-747-9003
Fax: 732-747-9004
cplacitella@cprlaw.com
Plaintiffs' Liaison Counsel

PLAINTIFFS' EXECUTIVE COMMITTEE:

Warren T. Burns
BURNS CHAREST LLP
500 North Akard Street, Suite 2810
Dallas, TX 75201
Tel: 469-904-4551
Fax: 469-444-5002
wburns@burnscharest.com

Richard Golomb
GOLOMB & HONIK, P.C.
1515 Market Street, Suite 1100
Philadelphia, PA 19102
Tel: 215-985-9177
rgolomb@golombhonik.com

Hunter J. Shkolnik
NAPOLI SHKOLNIK PLLC
360 Lexington Avenue, 11thFloor
New York, NY 10017
Tel: 212-397-1000
hunter@napolilaw.com

PLAINTIFFS' STEERING COMMITTEE:

Laurence S. Berman
LEVIN, SEDRAN & BERMAN LLP
510 Walnut Street, Suite 500
Philadelphia, PA 19106
Tel: 215-592-1500
Fax: 215-592-4663
lberman@lfsblaw.com

Timothy G. Blood
BLOOD, HURST & O'REARDON, LLP
701 B Street, Suite 1700
San Diego, CA 92101
Tel: 619-338-1100
Fax: 619-338-1101
tblood@bholaw.com

Sindhu S. Daniel
BARON & BUDD, P.C.
3102 Oak Lawn Avenue, #1100
Dallas, TX 75219
Tel: 214-521-3605
Fax: 214-520-1181
sdaniel@baronbudd.com

Jeff S. Gibson
WAGNER REESE, LLP
11939 N. Meridian St.
Carmel, IN 46032
Tel: (317) 569-0000
Fax: (317) 569-8088
jgibson@wagnerreese.com

Kristie M. Hightower
LUNDY, LUNDY, SOILEAU & SOUTH, LLP
501 Broad Street
Lake Charles, LA 70601
Tel: 337-439-0707
Fax: 337-439-1029
khightower@lundylawllp.com

Daniel R. Lapinski
MOTLEY RICE LLC
210 Lake Drive East, Suite 101
Cherry Hill, NJ 08002
Tel: 856-667-0500
Fax: 856-667-5133
dlapinski@motleyrice.com

Victoria Maniatis
SANDERS PHILLIPS GROSSMAN, LLC
100 Garden City Plaza, Suite 500
Garden City, NJ 11530
Tel: 516-640-3913

Carmen S. Scott
MOTLEY RICE LLC
28 Bridgeside Boulevard
Mount Pleasant, SC 29464
Tel: 843-216-9162

Fax: 516-741-0128
vmaniatis@thesandersfirm.com

Fax: 843-216-9450
cscott@motleyrice.com

Christopher V. Tisi
LEVIN PAPANTONIO
316 South Baylen St.
Pensacola, FL 32502
(850) 435-7000
ctisi@levinlaw.com